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PRECOCIOUS MENSTRUATION: OBSERVATIONS ON TWO CASES OF PUBERTAS PRECOX*

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The outstanding clinical manifestations of pubertas precox in the female are menstruation with associated development and early maturity of the body as a whole.

The average age for the establishment of menstruation in normal girls is between the thirteenth and fourteenth years. According to certain German statistics, menstruation occurs between the ages of 8 and 12 in 3.5 per cent of all cases. Lenz (1913) contends that menstruation should not be looked upon as precocious unless occurring under the age of 8 years. Novak (1921) says: "If menstruation begins and recurs regularly in a girl of less than 9 years of age, in this country (United States), it must be looked upon as precocious."

Lenz (1913) collected 130 cases of precocious menstruation occurring prior to the seventh year. Of this number 43 began to menstruate during the first year of life and 6 had their initial flow within the first month. In some cases menstruation continues regularly, save during pregnancy or lactation; however, this is the exception rather than the rule. The duration of the

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flow varies from 2 to 6 days, a variation comparable to that observed in normal adult women. These patients frequently complain of symptoms like those experienced by adult women at the menstrual period.

Conception is not infrequent in cases of sexual precocity. Lenz (1913) collected 10 cases of childbirth in girls before the age of 12 years.

Early development and maturity of the body as a whole usually occurs concomitantly with the appearance of precocious menstruation. Lucas (1888) reports the case of a girl who at the age of 7 years showed all of the signs of genitosomatic maturity and early menstruation. A tumor of the ovary was diagnosed and removed, following which all signs of adolescence and menstruation disappeared. The 7 year old patient reported by Brohl (1897) showed the development of a mature woman. In this instance, following the removal of a cystic ovary, menstruation ceased. The 5 year old patient of Harris (1917) ceased menstruating and regained her childish features following the removal of a carcinomatous ovarian teratoma. The 6 year old patient of Riedl (1904) had a uterus the size of that of a normal girl of 17 years. Removal of an ovarian sarcoma was followed by cessation of menstruation. The 2½ year old girl reported by Klein (1899) showed development of the vulva equal to that of a girl of 14 years. Stocker, quoted by Falta (1915), describes twin sisters, of whom one had been larger since birth. In the first, menstruation began before the end of the first year. The flow occurred regularly every 4 weeks, lasting 3 days. At 8 she had the size and appearance of a girl of 12 years; she was 139 cm. tall and weighed 34.75 kg., while the twin sister was 121 cm. tall and weighed 20 kg.

Osseous development usually parallels that of the sexual characters in cases of precocious menstruation. The bones are larger than normal for the age and ossification is further advanced than would be expected. The epiphyses unite early with the shafts, or are separated by only thin discs of cartilage. The pelvis in many cases resembles that of the fully developed woman. A case is reported by Wolff (1911) of a girl who at the age of 4 years had an osseous development equal to that of a normal girl of 10 years. Krabbe (1919) reported the case of

a girl seen at 13½ years of age. This patient began to menstruate during her first year and continued regularly every 4 weeks without interruption. Sex signs appeared early, the hips and thighs having always been prominent. She grew rapidly until the age of 7 years. Thereafter she did not grow in height and at the time of examination her lower limbs were strikingly short in relation to her trunk. The x-ray examination showed all the epiphyseal fissures of the upper and lower limbs completely grown together.

The precocious development of sex characters and somatic structures does not appear to cause a similar early appearance of psychic development. Leiner (1920), for instance, states that mental traits and habits are in no way precocious: "In fact, the subjects are of a low mental type. They speak, play and act in accordance with their true age. They learn well at school, but they show no 'old fashioned' way of thinking." Krabbe (1919), in discussing this point, asserts that in cases of "pubertas precox as in infantilism there may be a disassociation between somatic and psychic evolution. There are some cases in which they are parallel, but others where the psychic evolution is normal, while the somatic is either advanced or retarded."

Williams, quoted by Bell (1916), collected 11 cases in which ovarian neoplasms were associated with sexual precocity in female children. However, as pointed out by Leiner (1920), we should not draw the conclusion that all ovarian tumors in young girls necessarily lead to sexual precocity. Neither should it be assumed that all cases of precocious menstruation are the result of ovarian tumor masses. On the other hand, Novak (1921) asserts that "very few autopsies are recorded in cases of precocious menstruation in which there was no tumor present either in the ovaries or in the other internal secretory glands."

Undoubtedly many women are living who were subjects of pubertas precox and who will live to old age without the condition ever having been recognized. It is conceivable, as pointed out by Krabbe (1919), that early menstruation associated with precocious sex and somatic development "may be caused by an abnormally early function of the internal secretion of the ovaries, an early function which is not caused by a tumor, but is parallel to hypersecretion of the thyroid gland in Graves'

disease." A somewhat similar interpretation is given by Lespinasse (1922) for the appearance of pubertas precox in boys.

PRESENTATION OF CASES

Case No. 1, Nov. 29, 1924. Miss M. M., age 14 years and 11 months, white, student.

Complaints: Nervousness, over weight, shortness of stature and acne.

Family History: The father is 38 years old, 68½ inches tall and weighs 196 pounds. The mother is 39 years old, 65 inches tall and weighs 133 pounds. She states that her growth ceased between the ages of 10 and 15 years and that she grew in height after the age of 21. Her first menstrual flow occurred when she was 15 years old. The second period did not appear until the age of 19. She married at the age of 20, at which time she weighed 95 pounds, and has been pregnant 18 times. Three pregnancies lasted 6 months; the remainder, save two deliveries, terminated before the third month. She has been told that her child's condition resulted because of vaginal hemorrhages during gestation. A maternal uncle is a hunchback and 2 cousins are very short. There is no ascertainable history of congenital deformity, maldevelopment, insanity or feeble mindedness on either side of the family.

Clinical History: The patient was delivered at full term after a prolonged labor and weighed 9 pounds. She was breast fed. During her sixth month she had 10 convulsions. She was talking at 12 months and beginning to walk at 14 months.

The patient had a vaginal discharge of blood at 18 months. This was repeated every 90 days until about the age of 5 years. After this the periods occurred every 60 days until the age of 10, from which time they have appeared every 27 to 30 days. The menstrual flow has been variable in amount and duration. Until the age of 12 the periods were accompanied by excruciating pelvic cramps; head- or back-aches were not present. Premenstrual irritability has been of common occurrence. Masturbation was practiced a great deal during the third year.

Pubic and axillary hair appeared at the age of 5 years. Hair has never appeared on the face, trunk or abdomen. The voice became heavy with the appearance of the pubic hair and continued so until the age of 9, since which time it has become more nearly normal. The breasts enlarged rapidly during the fifth year and "at 9 she had the features of a completely developed small woman."

"M. was a handsome and healthy baby." She began to grow rapidly during her fifth year and continued to do so until the age of 9, since which time she has grown but little, if at all. During the period

of growth she required but little sleep and showed a high degree of interest in the affairs of others. Since the age of 9 she has taken on considerable weight, gradually lost interest in her surroundings and now requires considerable sleep.

Dizzy spells and stupor have been annoying symptoms for the past 3 years. She describes her sensations as follows: "The head feels like it is opened in the middle." Associated disturbances have never accompanied these "head attacks."

The patient has always been retiring, suspicious and afraid of people. She played with her dolls until a year ago. She has never shown anything but a healthy dislike for boys and only a moderate interest in girls. Her dislike for both boys and girls is partially explained because of their teasing her about her over-development. She is apparently somewhat conversant with matters of sex. According to her mother, the patient has never shown any signs of sex interest and is not affectionate. She has always been wilful, stubborn and hard to manage. She has been extremely nervous since one year of age. Her disposition has been decidedly more intractable of late. She starves herself in an effort to keep down her weight.

The patient did not enter school until the age of 9 because of nervousness. She has slowly made her grades and is now attempting high school work. Because of her poor school work she was seen on Jan. 9, 1920, by Dr. Stevenson Smith of the Psychology Department of the University of Washington. A part of Dr. Smith's report follows: "In response to mental tests, she is superior to approximately 28 per cent of children of her age. It appears that her precocious physical development and her mother's training, which has kept this always before the child's mind, has played some part in the development of the temperamental condition which is so obvious."

The patient as a child had several attacks of bloody dysentery. At the age of 9 years she had mumps, whooping cough, measles and scarlet fever. She had a second attack of measles at 11 years. She had chicken pox as a baby. Her tonsils and adenoids were removed at the age of 10 years. Acne has been present for several years.

Present Status: The menstrual periods are regular and associated at times with pelvic cramps. "Head attacks" are rather frequent. She is very irritable, stubborn and restless.

Physical Examinations: The patient is of a pudgy build and has the appearance of an overdeveloped and matured woman. The torso length is noticeably greater than the lower measurement. The neck is short and stout. The thighs are thick as also are the forelegs. There is moderate and general fat padding. The musculature is well developed and firm. The posture is good save for a slight droop of the shoulders (Fig. 1).

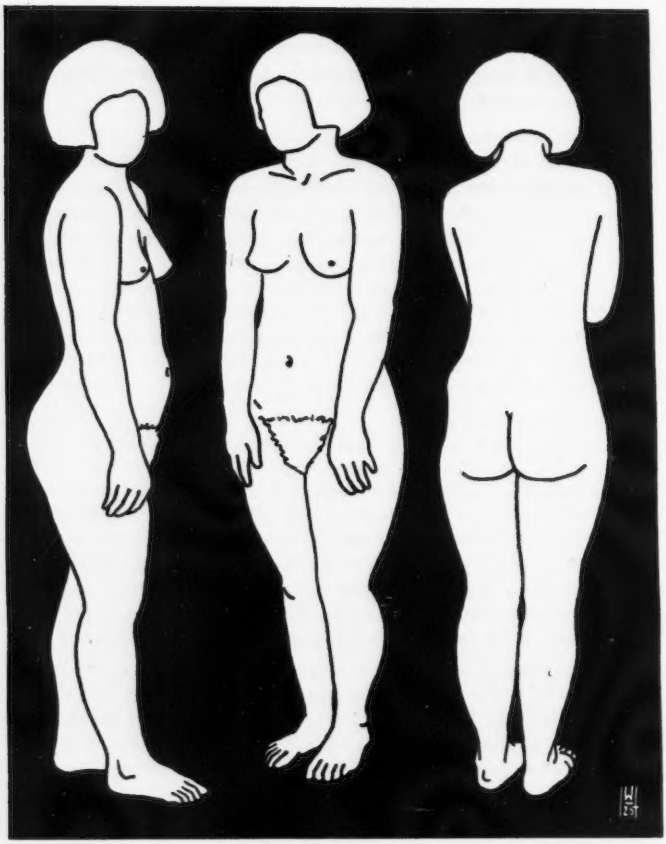

Figure 1. Outline drawing from projected photographic negatives of subject No. 1. Note the disproportion between the torso and lower lengths, largeness of the breasts and thickness of the thighs and forelegs.

Measurements:

Weight	48.6 kg.	107 pounds
Height	146.0 cm.	57⅝ inches
Span of arms	141.5 cm.	55⅝ inches
Torso length	79.5 cm.	31¼ inches
Plantar-symphyseal length	66.5 cm.	26⅛ inches
Head circumference—antero-posterior	54.5 cm.	21⅜ inches
Head circumference over vortex	34.5 cm.	13½ inches
Interpupillary distance	5.5 cm.	2⅛ inches
Neck circumference	31.5 cm.	12⅜ inches
Shoulder circumference	88.0 cm.	34⅝ inches
Axillary circumference	79.0 cm.	31⅛ inches
Bust circumference	76.5 cm.	30⅛ inches
Waist circumference at navel	65.5 cm.	25¾ inches
Crest of ilium circumference	79.5 cm.	31¼ inches
Trochanter circumference	89.5 cm.	35¼ inches
Elbow (Rt.) circumference	23.0 cm.	9 inches
Wrist (Rt.) circumference	15.5 cm.	6⅛ inches
Knee (Rt.) circumference	36.0 cm.	14⅛ inches
Ankle (Rt.) circumference	22.5 cm.	8⅞ inches

The skin is dry, pliable and has a good color. The hands, feet and axillae are moist. The finger and toe nails are well formed. The head hair is abundant, black in color, of fine texture, oily and has a high anterior attachment. The eyebrows meet to form a nasal brow. The axillae contain a luxuriant growth of dark hair. Pubic hair is abundant and of feminine distribution. There is a definite growth of hair over the forelegs and to a less degree over the forearms. The face and trunk are free from hair.

The cheek bones are prominent, the nose is pudgy and the lips are quite thick. The voice is harsh and low pitched; speech is normal. The teeth are all present save the third molars and have a dirty yellow color. The lower set are wired for correction of alignment.

The thyroid gland is not palpable. The abdomen, chest and heart show nothing abnormal on percussion and auscultation. The blood pressure is 130/70; the pulse rate 96; the buccal temperature 98.2° F. The arteries are soft and the veins small and well imbedded.

The breasts are well developed and firm. The left breast is noticeably larger than the right. The labia majora and minora are well developed. The vaginal inlet and the cervix are small. The body of the uterus and the adenexa could not be completely examined because of vaginismus and abdominal rigidity.

The neuro-muscular apparatus is entirely negative for pathological findings. Sensibility is normal. Careful ocular examinations made by Dr. Walter K. Seelye were negative save for the finding of reduced visual acuity, a condition not accounted for by any objective findings.

Laboratory Examinations: Blood: Wasserman reaction negative; hemoglobin, 97 per cent (Dare); red cell count, 4,176,000; white cell count, 13,000 one hour after lunch; differential count: polymorphonuclear cells, 58; small lymphocytes, 12; large lymphocytes, 27; eosinophile, 2; blood sugar, 120 mg. per 100 cc. of blood. The urine and vaginal smears are negative. The basal metabolic rate is +14 per cent; a second reading could not be secured.

X-ray Examinations: Epiphyseal lines are not demonstrable in the bones of the extremities. The frontal sinuses are extensive. There is marked irregularity in the density of the frontal bone. The third molars have not erupted. There is marked forward projection of the upper and lower frontal teeth. The sella turcica is small and the clinoids show no evidence of erosion. There are no shadows in the region of the pineal body.

Diagnosis: 1. Genitosomatic: Evolutio precox corporis and resultant dwarfism. 2. Psychic: Mentally inferior to approximately 75 per cent of individuals of her age. 3. Reduced visual acuity unaccounted for by objective findings. 4. Acne simplex.

Case No. 2, Jan. 1, 1925. Miss C. M., age 18 years, white, student.

Complaints: Painful menstruation, headache, pains in the legs and back and marked deposition of fat over the trochanteric regions.

Family History: The patient's mother began to menstruate at the age of 12 years and attained her present height of 66 inches prior to the age of 14 years. Her periods were not regular until after the birth of her first child. An only sister of the patient began to menstruate at the age of 14 years. The family history does not disclose insanity, tuberculosis, congenital malformations or growth disturbances.

Past History: The patient was delivered normally at full term and weighed 6 pounds. She was walking and talking at 14 months. The deciduous teeth were erupted "at the usual time." She weighed 19 pounds on her first birthday. During her second summer she contracted cholera infantum, measles and chicken pox. As a result of this she weighed but 21 pounds on her second birthday. "Her hair became thin and straggly," she was puny, sickly and poorly nourished and continued to have intestinal trouble each summer until the age of 5 years. At the time she started to school she began to increase in weight; her hair began to grow rapidly and became glossy. Moderately severe gastrointestinal disturbances appeared again during her seventh year and markedly interfered with her school work.

She injured her sacrum and coccyx when 8 years of age and one year later took treatment for "deformity at the tip of the backbone." Shortly following this injury she began to take on weight and grew rapidly in height. Growth continued rapidly until the age of 13 years, since which time she has continued to take on weight, espe-

cially about the thighs. A few months preceding the rapid bodily development, that is, during the eighth year, the patient had a severe attack of pain in the right iliac fossa associated with high fever, nausea and vomiting. She experienced a similar attack at the age of 15 years, at which time the condition was diagnosed as acute appendicitis.

The breasts and external genitalia began to develop rapidly during the summer prior to her ninth birthday. Pubic and axillary hair appeared during her eighth year and "she was fat all over." At the age of 9 years and one month she began to menstruate. The initial flow was not preceded by prodromal symptoms, but was associated with severe headaches and pelvic cramps. Subsequent periods, which appeared regularly, were preceded by severe headaches and cramps and accompanied by backache and legache. The average duration of the flow has been 3 days; the amount of the flow has always been moderate. The headaches, which were of a migraninous nature, usually ceased with the establishment of the flow. At the age of 11 years the voice became heavier and had the pitch and timbre of an adult voice.

The patient weighed 133 pounds at the age of 12 years. Since the age of 13 years, at which time she attained her present height, she has developed abnormally about the hips, especially over the thighs.

The patient had whooping cough when 3 years old, mumps at 7 and at 10 an attack of pleurisy. At 13 years she had several attacks of tonsilitis and developed a "weak heart." The tonsils and adenoids were removed the same year. At 14 years she had a rather severe attack of influenza and the heart developed a murmur. She has never had convulsions or fainting spells. The eyes have been sensitive to light since early childhood. She has made her school grades easily.

Present Status: Premenstrual headaches have been getting progressively worse for the past 5 months. They usually begin from one to five days before establishment of the flow and are located along the posterior part of the neck, at the base of the skull and behind the eyeballs. These headaches usually appear in the morning and are associated with slight nausea. At times vision is blurred; however, blindness or diplopia have never occurred. The onset of the period of headaches is usually preceded by a few days of marked somnolence, general weakness and fatigability. Establishment of the menstrual flow is followed by complete relief from headache.

The menstrual flow lasts on the average only three days and is "only average in amount." Because of the severity of pelvic cramps, backache and pains in her hips and legs during the flow, she is forced to go to bed and at times requires opiates. For the last three months she has experienced heavy bearing-down pains, backache and pains in the legs, especially the right, following cessation of the flow and during the intermenstrual period. She is now subject to severe

cramps and drawing pains in the legs. These cramps and the backache are decidedly more pronounced on the right side. The right leg goes to sleep a great deal.

Considerable belching after meals and obstinate constipation have been noticed since the appearance of the premenstrual headaches.

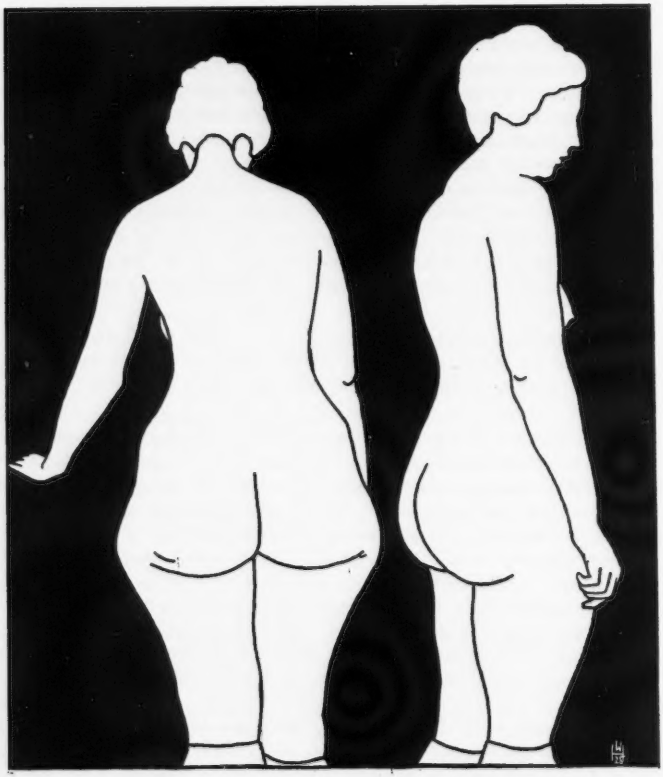

Figure 2. Outline drawing from projected photographic negatives of subject No. 2. Note the degree of fat padding over the trochanteric regions.

Sleep is restless because of the backache, which is relieved only by placing her arms under the small of the back. Her strength is excellent; however, she is restricted in her activities because of the constant distress in the back and legs. She wears glasses to read with.

The patient is emotionally sensitive and very particular in the choice of her friends. Apparently members of the opposite sex hold

very little interest for her inasmuch as she has "never had a love affair." She complains of dreaming a great deal, becomes frightened in her dreams and talks considerably in her sleep.

Physical Examinations: The patient shows a marked disproportion of fat distribution, there being an excessive accumulation of adipose tissue over the trochanteric regions (Fig. 2). The posture is good. There is some falling of the pedal arches.

Measurements:

Weight, without clothes	71.6 kg.	157 pounds
Height	162.7 cm.	64.0 inches
Span of arms	166.0 cm.	65⅝ inches
Torso length	78.5 cm.	30⅞ inches
Plantar-symphyseal length	84.2 cm.	33⅛ inches
Circumference of head over vertex	36.3 cm.	14¼ inches
Antero-posterior circumference of head	55.6 cm.	21⅞ inches
Interpupillary distance	5.5 cm.	2⅛ inches
Neck circumference	34.0 cm.	13¼ inches
Shoulder circumference	95.0 cm.	37⅜ inches
Axillary circumference	81.0 cm.	31⅞ inches
Circumference of bust	84.0 cm.	33 inches
Circumference at level of navel	69.0 cm.	27⅛ inches
Circumference at crest of ilium	93.0 cm.	36⅝ inches
Circumference at level of symphisis	106.0 cm.	41¾ inches
Circumference over trochanter	122.0 cm.	48 inches
Circumference of right elbow	24.6 cm.	9½ inches
Circumference of right wrist	16.0 cm.	6¼ inches
Circumference of right knee	43.0 cm.	17⅛ inches
Shoe size		No. 6½
Glove size		No. 6½

The skin is soft, pliable, moist and has an excellent color. The hands and feet are livid and moist. The cheeks are florid. Hair development is luxuriant and of typical feminine distribution. Hair is quite prominent on the forearms and legs. The hair follicles on the forelegs are large and cause the skin to feel rough to the touch.

The teeth are crowded, in good alignment and have a clear bluish color. The thyroid gland is palpable and soft.

The blood pressure is 130/82. The pulse is regular but has a high rate, 96 per minute. The heart and lungs are negative upon percussion and auscultation.

There are no disturbances of the neuromuscular apparatus or of the sensibilities.

The mammary glands are well developed. The labia majora and minora are well developed. The uterus is of moderate size and freely movable.

There is considerable tenderness over the right lower quadrant of the abdomen. Pressure over the sacral joint causes considerable distress and pressure over the right hip joint causes pain throughout the entire right leg.

Laboratory Examinations: Blood: Wasserman reaction negative; blood sugar, 130 mg. per 100 cc. blood; hemaglobin, 95 per cent (Dare); red cell count, 4,944,000; white cell count, 7,000; differential count: polymorphonuclear cells, 59; small lymphocytes, 28; large lymphocytes, 13. The urine contains a faint trace of albumin. The kidney function test gives a return of 70 per cent of the dye along with an output of 550 cc. of urine in 2 hours and 15 minutes. The basal metabolic rate is +12 per cent.

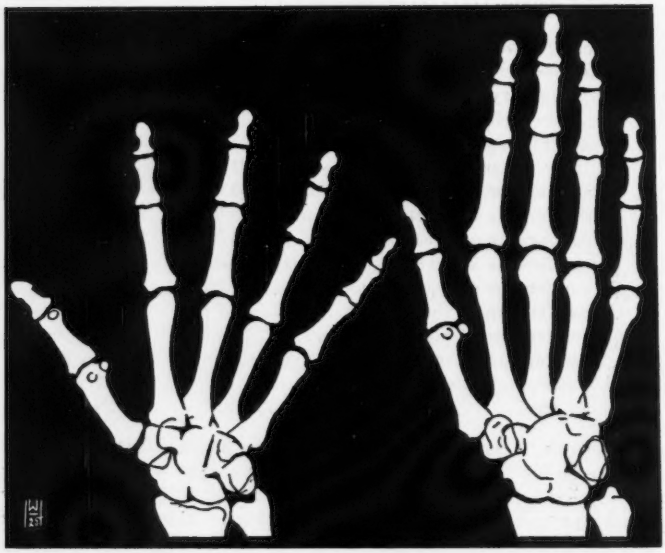

Figure 3. Outline drawing of x-ray plates of the right hand of subjects No. 1 (A) and No. 2 (B). Note the differences in size and general structure of the two hands. The epiphyses in each instance are completely closed.

X-ray Examination: The epiphyses of the long bones and those of the hands and feet are closed, as are those of the crest of the ilium. The frontal sinuses are very small. The sinuses are clear. The sella turcica is large; the posterior clinoids show some haziness of outline. The plate of the lumbar and pelvic regions shows no bony abnormality. The pelvis is typically feminine in structure.

Diagnoses: 1. Genitosomatic: Pubertas precox; dysmenorrhea

and trochanteric fat padding. 2. Chronic appendicitis and constipation. 3. Fallen pedal arches. 4. Acne simplex.

Operation: March 26, 1925. The stomach, gall bladder and liver are normal. The duodenum is large but free from adhesions and congenital bands. The colon contains much fecal matter. The cecum and terminal ilium are freely movable. The appendix occupies a retroperitoneal position and is free from adhesions. Two concretions occupy the lumen of the appendix. The right kidney can be moved about 5 cm.; the left 2 cm. The kidney borders are smooth and even. No masses can be palpated in the suprarenal bodies.

The uterus is of moderate size and quite soft. The fallopian tubes are small and their fimbriated ends normal in appearance. The right ovary is of normal size and contains a corpus luteum of recent origin at the upper pole; the lower pole is decidedly sclerotic. The left ovary is very small, sclerotic and has the appearance of a senile organ.

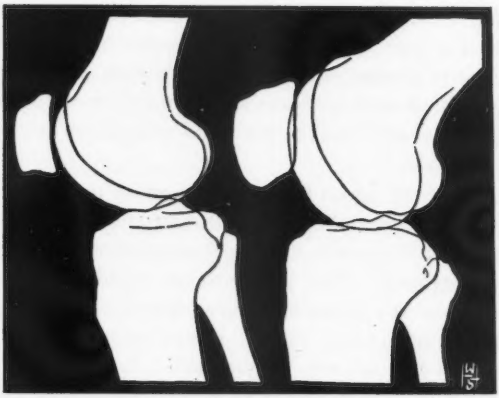

Figure 4. Outline drawing of x-ray plates of the right knee of subjects No. 1 (A) and No. 2 (B). The epiphyses in each instance are closed.

DISCUSSION

It is probable that the evolution of precocious puberty depends on the gonads; that is, hypergenitalism may be looked upon as the causative factor in the establishment of functional early puberty. However, the premature development of sex and sex characters has been observed associated with pathological processes in organs of internal secretion other than those of the gonads. Such associations are so constant that definite clinical syndromes are described as the result of tumor forma-

tions not only in the gonads but also in the pineal body and suprarenal glands. The precocious appearance of sex and sex characters also has been observed in the absence of demonstrable disorders of these various organs.

The appearance of sex characters in the preadolescent female similar to those which appear in the male at puberty, that is, heterosexual characters, and the precocious appearance of masculine characters and virilism in the preadolescent male, appear constantly as the result of tumors of the adenomatous type (hypernephromata) in the suprarenal cortex. Clinically such cases are described as virilismus when occurring in the female and pubertas precox virilis when present in the male. Such patients should not be classed specifically as cases of pubertas precox for the reason that they are not "functionally capable of generation"; the girls show infantile development of the breasts and genital organs and they do not menstruate, and the boys are said not to produce spermatozoa. Tumors of the suprarenal cortex associated with developmental anomalies of the sex characters appear approximately five times more often in the female than in the male.

Tumors of the pineal body, usually of the teratomatous type, appearing in the preadolescent individual, have been observed associated with the precocious appearance of sex characters and bodily overgrowth. The pineal-gonad syndrome frequently described as macrogenitosomia precox appears more often in the male than in the female; indeed, it was formerly believed that such a condition exists only in the male.

At the present time precocious menstruation is considered under one of three forms depending upon the degree of associated somatic development: 1. *Menstruatio precox,* or the discharge of blood at regular intervals from the generative tract; 2. *Pubertas precox,* or that complex of anatomical and physiological changes in the external and internal generative organs of girls characterized by certain changes in the breasts, the distribution of hair, etc., together with the appearance of certain periodic processes of which menstruation is the most important; 3, *Evolutio precox corporis,* or that array of symptoms associated with an accelerated development of the reproductive system, together with a premature stimulation of the bodily growth.

The latter shows itself in an increase in the size as well as the weight of the body, an accelerated growth of the entire skeleton, and a premature ossification of the epiphyseal cartilages (Novak, 1921).

A diagnosis of evolutio precox corporis is warranted in the first case in that sexual and somatic maturity appeared much earlier than in the average girl. Menstruation, although established in this case at the age of 18 months, was not regular in appearance until the tenth year or following the time of cessation of growth. In fact, this case may be looked upon as one of menstruatio precox up to the age of 5 years. During the fifth year there appeared pelvic and axillary hair, enlargement of the breasts, deepening of the voice and the beginning of rapid growth which continued until the ninth year. Such an association of developmental phenomena together with the fact that the status of the osseous system at the age of 14 years and 11 months is equal to that of the average 18 year old girl sufficiently fulfills the requirements of the diagnosis given. In addition there is the low degree of mental development described by Leiner (1920) as usual in such cases.

Puberty in its entirety as seen in the normal girl is not established in the present case, in that libido has not appeared. A further lack of proof of complete puberty is the inability to know whether or not the patient is functionally capable of generation. The appearance of menstruation, however, is strong presumptive evidence of ovarian maturity.

The possibility of suprarenal disturbances may be dismissed as unlikely. The typical distribution of hair, the absence of pigmented areas of the skin, the marked development of the breasts, the absence of hypertrophy of the clitoris and the presence of menstruation constitute sufficient evidence for such a conclusion.

Evidence of pineal involvement is entirely lacking. There is no evidence of hydrocephalus, brain tumor or eye muscle disturbances, all of which are present in the pineal-gonad syndrome.

The shortness of stature differs markedly from that seen in pituitary and thyroidal disturbances in that the epiphyseal lines are completely closed. The patient's measurements are of the infantile type in that the torso is longer (13 cm.) than the

plantar-symphyseal length, and the spread of the arms less (4.5 cm.) than the height. Such proportions are quite the opposite of those observed in cases of eunuchoidism or gigantism.

Absolute proof of the gonadal origin of pubertas precox in this case is not available, neither is there definite proof of the absence of lesions in the suprarenal cortex or pineal body. Specific pathological evidence is wanting; however, the clinical picture is such as to warrant the diagnosis given.

The second case is diagnosed as one of pubertas precox. Menstruation, in this instance, was established at an age (nine years and one month) that might not be considered as precocious for the appearance of sexual characters. However, the definite series of developmental changes occurring during the eighth year are indicative of both somatic and sexual precocity. These developmental changes appeared suddenly in an individual who, up to that time, had been a puny child. A peculiar series of events antedated the bodily changes; namely, a fall which gave rise to considerable pain in the region of the sacrum for at least one year and an attack of acute appendicitis. Following these she took on weight and began to grow rapidly. Growth continued until the thirteenth year, at which time she attained her present height of 162.7 cm. She was "fat all over" at 9 years and at 12 she weighed 133 pounds. The breasts developed rapidly and hair appeared in the axillae and on the mons veneris during the eighth year. The voice became heavier at the age of 11 years.

The initial menstrual flow occurred one month after her ninth birthday. Later the periods were preceded by prodromal symptoms and accompanied by much distress. Menstruation since its onset has occurred regularly each month. Quite the opposite condition occurred in the first patient.

The development of the generative organs, the distribution of hair, the presence of menstruation, and the lack of intracranial symptoms, in this case, are such as to rule out the likelihood of pathological processes in the suprarenal cortex or pineal body. Further, it was possible to prove the absence of masses in the suprarenal bodies and ovaries during an operation for the removal of the appendix. As for the ovaries, there

appeared to be a high degree of fibrosis (sclerosis) rather than the presence of irritating masses.

Nothing definite is known concerning the time of closure of the epiphyses for the reason that studies on this point were first made at a time when the epiphyses are normally closed. However, there is no evidence of dwarfism. The body proportions differ materially from those of the first patient; the torso length is less (5.7 cm.) than the plantar-symphyseal length and the spread greater (3.3 cm.) than the height. These proportions are eunuchoidal in character. Because of these findings we may assume that the epiphyses were not prematurely closed; at least they were not closed until the bodily proportions had attained definite noninfantile proportions.

To judge from reported cases of pubertas precox, obesity is of common occurrence; however, obesity of specific regions has not been consistently reported. Krabbe (1919) speaks of his subject as always having been wide through the hips and thighs. The second subject presented was fat all over at the time she began to menstruate and continued heavy throughout her growth period. Following attainment of her present height the general obesity disappeared and the localized trochanteric fat padding became prominent. This accumulation of fat over the tronchanters continued to increase until at the time of examination she measured 27 cm. more around the trochanters than around the shoulders.

Because of the eunuchoidal nature of the osseous development and the peculiar distribution of fat we are led to assume the possibility of a hypogonadal condition in spite of the early appearance of menstruation and rapid bodily growth. The severe and persistent degree of dysmenorrhea might also be looked upon as indicative of a condition of hypoövarianism. Such apparently contradictory conclusions may be reconciled in that the peculiar fat distribution occurred only after attainment of height maturity and the osseous development occurred as the result of factors for bone elongation, the force of which was sufficient to delay epiphyseal closure until a nearly normal chronological age.

Appendicitis, whether causative or coincident, in this case, must be considered seriously for the reason that removal of

this organ was followed by immediate relief from excruciating backaches, bearing-down pains, pains in the legs, uterine cramps, headache and somnolence which occurred either preceding, during or following the act of menstruation. Surgically, sufficient disturbance of the generative tract was not found to account for this series of symptoms. The uterus, tubes and ovaries were free from adhesions and inflammatory processes; however, the appendix did contain two fecoliths. The question naturally arises as to whether or not the marked degree of dysmenorrhea was the result of appendiceal disturbance or the result of gonadal disorder. It appears that had dysmenorrhea been the result of gonadal disturbances, the removal of the appendix would not have resulted in the immediate relief of these symptoms. However, the presence of a "colicy" appendix might have been sufficient to precipitate the array of disturbances at a time of general pelvic engorgement or during the menstrual period. Such an assumption would demand the presence of such an irritant from the very beginning of menstruation. Such an excitant might have had its origin in the severe attack of appendicitis and the sacral injury, both of which occurred preceding the establishment of menstruation. Whether or not these two accidents were instrumental in exciting precocious menstruation, of course, is impossible to say. Inasmuch as definite disorder of the ovaries was lacking, the relation between the appendiceal condition and the appearance of dysmenorrhagic menstruation becomes of more importance. Irrespective of such a possible relation it can be said that precocious menstruation and the establishment of sex characters associated with the somatic development was not the result of demonstrable tumor formations in the ovaries or suprarenals. Of course a tumorous condition may have been present; however, if present it left no signs by which it could be recognized by gross inspection at operation. We may conclude that this case is representation of those cases of early menstruation due to factors other than tumor masses in the ovaries.

CONCLUSIONS

1. A study of two cases of precocious menstruation is presented.

2. Consideration of these two cases fails to reveal any defi-

nite causative factor for the appearance of precocious menstruation.

3. Early menstruation, as evidenced by the second case presented, may occur independent of demonstrable gross pathology of the ovaries.

BIBLIOGRAPHY

Bell, W. B.: The sex complex. N. Y., 1916. Wm. Wood & Co., 233, pp. 8°.

Brohl: Ovarialkystome in 7-jähriges Mädchen, Zentralbl. f. Gynäk. (Leipz.), 1897, **21**, 113.

Falta, W.: The ductless glandular diseases. Transl. & ed. by M. K. Meyers, Phila., 1915, P. Blakiston's Son & Co., 692 pp., 4°.

Harris, R. H.: Carcinomatous ovarian teratoma with premature puberty and precocious somatic development. Surg. Gynec. & Obst. (Chicago), 1917, **24**, 604-611.

Klein: Ein Fall von Pubertas praecox. Deutsche med. Wchnschr. (Leipz. u. Berl.), 1899, 47.

Krabbe, K. H.: Early synostosis of the epiphyses with dwarfism in pubertas precox. This Journal, 1919, **3**, 459-466.

Leiner, J. H.: Pubertas precox with especial attention to mentality. This Journal, 1920, **4**, 369-380.

Lenz, J.: Vorseitige Menstruation, Geschlechtsreife und Entwicklung, etc. Arch. f. Gynæk. (Berl.), 1913, **99**, 67-144.

Lespinasse, V. D.: The testicle as a gland of internal secretion. Endocrinology and Metabolism. D. Appleton & Co., N. Y., 1922, **2**, 491-523.

Lucas, R. C.: Tumor in the right ovary in child aged seven years, associated with precocious puberty; ovariotomy; cure. Tr. Clin. Soc. Lond., 1888, **21**, 224-227.

Neurath, H.: Die Vorzeitige Geschlechtsentwicklung (Menstruatio praecox). Wien. med. Wchnschr., 1909, **59**, 1301-1313.

Novak, E.: Menstruation and its disorders. Gyn. & Obst. Monographs, N. Y., 1921, D. Appleton & Co., 357 pp., 8°.

Riedl, H.: Menstruation praecox und Ovarialsarkom. Wien. Klin. Wchnschr., 1904, **9**, 942.

Wolff, B.: Zur Kenntniss der Entwicklungsanomalien bei Infantilismus und bei vorzeitiger Geschlechtsreife. Arch. f. Gynæk. (Berl.), 1911, **94**, 542-579.

THYROID STUDIES I. THE DISTRIBUTION OF GOITRE AMONG INDIANS; ITS BEARING UPON THE ETIOLOGY

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"Goitre" is here used in its broad sense to indicate all thyroid enlargements. Even a meagre review of the literature will show the complexity of this condition by the numerous theories offered. The outstanding factors concerning the etiology which seem to have the most accurate scientific support are iodine deficiency [Marine and co-workers (1)] and the accumulation of toxic products [McCarrison (2) and others (3, 4, 5, 25)].

Marine and his co-workers have shown the great affinity of the thyroid for iodine (1). Many investigators have shown the constant presence of iodine in thyroid tissue. Iodine as such has been used with favorable results for treating goitre since the early part of the nineteenth century (1). In 1917, Marine, Kimball, Lenhart and Rogoff demonstrated the beneficial effect of iodine as a prophylactic in cases of thyroid instabilities. Since then this work has been repeated in Switzerland and also in this country (9). The results point strongly toward a relationship between thyroid disturbances and the iodine obtainable. An uneven distribution of iodine throughout the country suggests that goitre districts are probable iodine deficiency districts. The early works of Forbes and Beegle (6) on iodine distribution throughout the United States needs supplemental information because of later improved methods for iodine determination. McClendon (7, 8) has undertaken a recent study of iodine distribution by an improved technique. In this preliminary report he shows a striking parallelism between iodine distribution and goitre districts. These results are indicated in Figure II. The statistics for goitre incidence used by McClendon are those

compiled by the War Department and are the only ones available for the country at large.

Many investigators have shown the effect of various toxic materials upon the thyroid gland. McCarrison found that fecal contamination could produce thyroid changes (2). Burget produced changes in the histological appearance of the gland by unhygienic surroundings (3). Sows which are fed a high protein diet, thus increasing intestinal putrefaction, gave birth to goitrous pigs (11). Therefore not only the iodine assimilation but toxic materials as well have been shown to affect this gland.

It appeared to us that an approach toward the selection of fundamental factors involved might be made by a detailed study of the incidence and distribution of the disease. Such a study would indicate the location of goitrous regions. The factors peculiar to these regions could then be studied. Many limited survey studies have been made and goitre districts of this country as well as the world at large have been mapped out, yet it seems that no satisfactory explanation has been given which will apply equally to all of these districts. A complete survey of the incidence of goitre in this country would be invaluable. Such an undertaking is beset with numerous difficulties. We believe that a contribution might be made by undertaking a goitre survey of one class of people, inclusive enough to be indicative of the whole country yet small enough to make possible a careful survey. A class should be chosen which is made up of un-nomadic inhabitants of the localities being investigated. This class must be one that would not show any racial immunity to the disease.

The native North American Indians seem to meet all requirements very well. This race is numerous enough to give indicative figures of the localities being investigated. Moreover, the Indian population is not too massive for an accurate survey, especially since the tribes are cared for on reservations under supervision. A study of Indian life shows the un-nomadic characteristics of the race. This is probably more pronounced with the Indian than with any other class of American people (12). Consequently these people have not come under the influencing factors of outside regions. Since the Indians have

goitre and the incidence is very high in some districts, racial immunity does not exist.

Our information concerning the incidence of goitre among the Indians was kindly furnished by Doctor R. E. L. Newberne, Chief Medical Supervisor of the Indian Commission. A questionnaire was sent throughout the Indian population during the Fall and Winter of 1922-1923. The data were gathered by the respective Indian physicians, compiled by the Indian Commissioner's office and forwarded to us. The results obtained from this survey are shown in Figure I, the incidence of goitre being arranged according to States.

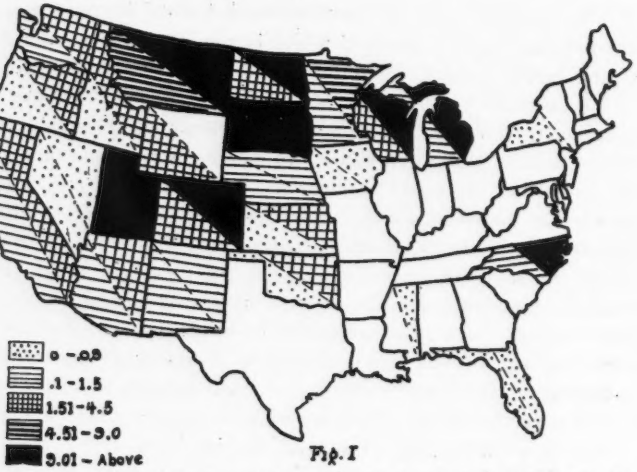

Figure I. Indian surveys. Goitre incidence by states. Lower and left hand half indicates incidence of goitre as shown by the survey of 1908 (Hrdlicka). The upper and right hand half indicates the incidence as shown by the survey of 1923. States left blank indicate states from which no statistics were obtainable.

A complete goitre survey among the Indians was compiled in 1908 by Hrdlicka (13), who was working, at that time, in conjunction with the Indian Commission. These data are shown in Table I; they give the proportions per thousand of population for the various tribes. We have rearranged these figures to show the incidence of goitre according to States.

A study of the results of these Indian surveys shows goitre to be present among this race. It also bears out the generally reported observation that goitre in the United States is regional

TABLE I

Goitre among Indians. Proportions per thousand of population.

Tribe	State	Per 1000	Tribe	State	Per 1000
Blackfeet and Sioux	S. Dak.	61.4	Shoshoni and Arapaho	Wyo.	3.6
Ute	Utah	35.4	Mission Indians	Calif.	3.1
Oneida	Wis.	26.7	Apache (White Mt.)	Ariz.	2.9
Cheyenne	Mont.	25.6	Sioux (branch)	S. Dak.	2.9
Sioux	S. Dak.	14.3	Sioux (branch)	S. Dak.	2.9
Menominee	Wis.	10.9	Sioux (branch)	N. Dak.	2.8
Indians (Genoa School)	Nebr.	10.0	Hopi	Ariz.	2.1
Sioux (branch)	S. Dak.	7.8	Oneida	Wis.	1.9
Chippewa	Mich.	6.7	Cheyenne	Okla.	1.8
Crows	Mont.	6.6	Coeur d'Alenes	Wash.	1.7
Indians (Ft. Berthold)	N. Dak.	6.6	Piegan	Mont.	1.5
Southern Ute	Colo.	5.6	Pawnee	Okla.	1.6
Rio Grande Pueblos	N. Mex.	5.3	Yuma	Calif.	1.5
Sioux (branch)	S. Dak.	4.3	Cherokee	N. Car.	1.4
Sioux (branch)	Mont.	4.2	Apache	S. Colo.	1.3
Navajo	Ariz.	4.1	Sioux (branch)	S. Dak.	1.2
			Sioux (branch)	S. Dak.	1.1

From Bull. 34 Bur. Am. Ethnology. Physiological and Medical Observations among Indians. Hrdlicka.

in distribution. These regions are considered to be in the Pacific Northwest, the North Central States, Great Lake District and in the Appalachian Highlands. Thus, excepting the Pacific Northwest, the incidence among Indians is roughly parallel with the incidence among the population as a whole. It will also be further seen that goitre has been increasing among the Indians. This increase seems to be quite general although more pronounced in the goitre regions. The number of cases reported in 1908 was 376 for an Indian population of 125,000, giving an incidence of three per thousand. In 1923, this increased to 3092 cases for a population of 189,200, giving an incidence of 16.3 per thousand.

In the light of Marine's work to which reference has been made it would seem most logical to turn to a possible iodine deficiency as the etiological basis for this affliction. While definite experimental data are incomplete to show this factor to be responsible for goitre development, the prevention work with iodine is highly suggestive. If this deficiency is the cause, districts with a scarcity or absence of iodine must be present and these districts must coincide with the goitre districts. McClendon's work points in this direction but, as the author states, it is far from complete (7, 8).

Because of the lack, then, of complete information concerning iodine distribution, attention may be turned to these conditions that may influence its deposition. Iodine is found in small quantities on the earth's crust widely distributed, but by far in greatest amounts in the sea. It is the most sparingly deposited of the halogen salts (14). Analysis of sea-water shows iodine to always be present, the amount usually being stated as 100 mg. per litre. Iodine is found in nature almost exclusively as sodium iodide, the most soluble of natural salts. This salt is about five times as soluble as sodium chloride. This difference of solubility can easily account for the abundance of sodium chloride and the scarcity of sodium iodide.

When salts are deposited the most insoluble will be the first to reach saturation and consequently deposition (16). On the contrary, the most soluble will be the last deposited. Thus the most soluble salt will continuously be kept in solution if more water is added to the evaporating body of liquid and also it will be the soluble salt which will run off if the supernatant fluid escapes. Therefore, as Hayhurst has indicated (14), iodine is scarce upon the earth's crust because: (1) "it has been carried off by supernatant fluid during the process of the drying-up of saline waters; (2) the dissolving-out process that occurs as a result of the percolation of the rains and subterranean waters carries out the soluble salts (iodine); (3) the pent-up deposits and brines have been perfused so long by fresh waters as to carry away their more soluble constituents."

Geographic districts that would be favorable to iodine deficiency should therefore be those regions which show at least some of the following meteorological and geological characteristics. First, they must have been thoroughly washed by fresh water perfusion. This may have been caused by the washing from the melting of old glaciers, the percolation of abundant rainfall or the perfusion by subterranean waters. Secondly, the slope of the country must be such that the water will rapidly flow off, thus removing the soluble constituents from the region. Thirdly, these regions farthest removed from the sea would have the least opportunity for replenishing the iodine lost.

The goitre districts of this country are situated in such regions. The Pacific Northwest, although of relatively recent

geologic origin, has been, nevertheless, subjected to many washings. The flow from the old glaciers passed over this country. Again we find great fresh water perfusion as the result of heavy yearly precipitation. Notwithstanding that this country is along the sea coast, its slope is such as to favor rapid movement of both surface and subterranean waters. No other sea coast of the United States has the slope or the precipitation this coast shows. Therefore iodine loss might be expected to be greater than any iodine deposition from sea air. Consequently iodine deficiency can be expected.

The Rocky Mountain States are in a rugged country. Although their rainfall is but moderate, the slope offers rapid drainage. As has been indicated by Hayhurst (14), the mountains are the first to lose their supply of iodine. The glacier water also washed these soils. Therefore this district should also show an iodine deficiency.

The Great Lakes territory was influenced more by the glacier period than any of the vicinities previously mentioned. The precipitation of this district is moderate and the slope gentle. Consequently it would seem that past periods have had more bearing upon the depletion than present conditions. However, the continual fresh water perfusion that is now taking place makes the depletion more complete. On the other hand, the Appalachian Highlands are apparently affected more by percolating rains and fresh water perfusion. It may be pointed out that the area in western North Carolina shows the heaviest rainfall of the East. This district is also mountainous, which insures rapid drainage. Thus, if our hypothesis is correct, other iodine deficiency areas should be located in these regions.

The South appears to be comparatively free from goitre. This part of the country has a gentle slope. The waters which arise in the North, particularly the North Rocky Mountain, North Central and Great Lakes States, flow down over the gentle slope of the South. During the course of this flow the more soluble substances of the soil will be carried off from the North, only to be deposited in those regions where evaporation makes the concentration sufficient. As evaporation is continually taking place and as the Southern States have the gentle slope which retards the movement of the flow, iodide salts could be

deposited in these regions. Moreover, as the slope at the sea coast is much less abrupt in both the East and South, iodine deposited from the sea air should not be washed out as rapidly as in the Northwest. The Southwestern States are the most arid of the United States. Although this district is somewhat mountainous, the geographic formation is more of a high plateau. As a result of these conditions the percolation due to rainfall and the fresh water perfusion is lacking. The Southern States were not affected by the glacier period and consequently the South should be a land rich in iodine.

Previously it was stated that the results from the Indian survey (1923) indicated a parallelism of the incidence of goitre among the Indians and the country at large. Exceptions, however, will be noted as occurring in the Pacific Northwest. In this area goitre was practically absent from the Indians in 1908 and at the present time is much less frequent than among the white race. Three explanations may be offered for this variation. The primary cause, apparently, is found in the Indian diet. The American Indian, like most aborigines, uses those articles of food most easily obtained (12). Among the chief substances of diet of the Northwest Indians is salmon, and to a lesser degree other sea foods. Salmon composes a very large part of the diet not only during the fishing season, but it is eaten in the dried form a greater part of the year. Fishing is universal among these Indians and even the inland tribes obtain this sea food. Jordan (20) has shown that salmon run to the headwaters of the Northwest streams to a distance of 2500 miles. It has been shown [Cameron (21)] that "all sea species of animals contain iodine." The iodine obtained from the diet of salmon by the Indians should, on the basis of Marine's results, serve to prevent the development of goitre. Attention may also be called to the fact that the Indian of the North depended also in a large part on game for food. Unlike the white people, the Indians utilized the whole animal, which would include thyroid gland in the diet. The average amount of iodine found in thyroid tissues varies from 0.050 to 0.777 mg. per gm. of fresh tissues (1), depending upon the activity of the gland. Even so small an animal as the rabbit would furnish about 0.155 mg. of iodine. As it has been shown that 100 to 200 mg. of iodine twice

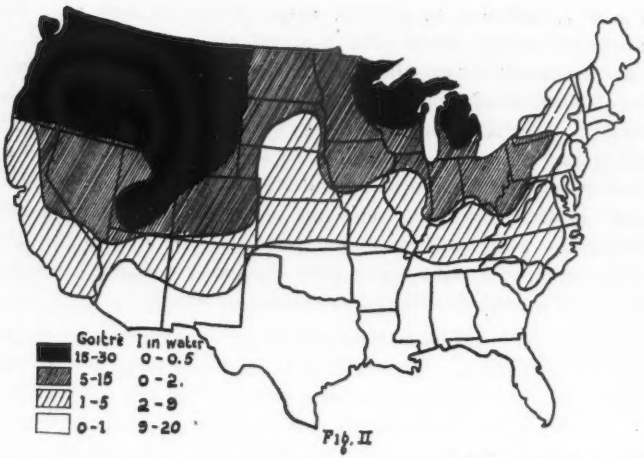

Figure II. Shows the incidence of goitre per thousand as determined in "Defects Found in Drafted Men, War Department, 1920," and the amount of iodine in the water. The curves have been rounded off. (McClendon, 7.)

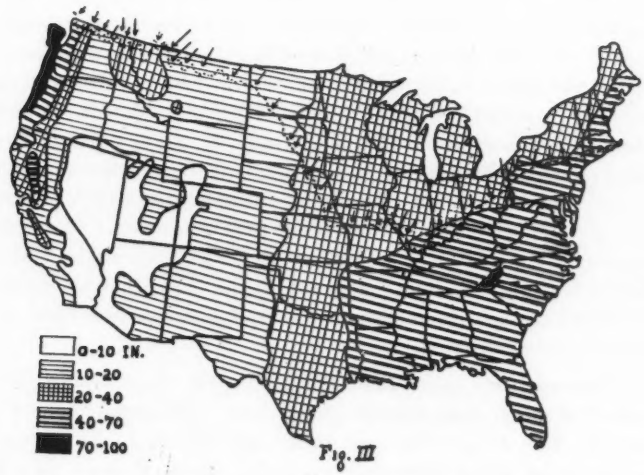

Figure III. The shaded areas show the annual precipitation of the United States (U. S. Department of Agriculture, Weather Bureau, Bull. Q, Climatology of the United States, by A. J. Henry). The dotted line indicates the old glacier line from which waters flowed over the northern part of the United States. (Geology by Chamberlain and Salisbury.)

a year is sufficient to prevent simple goitre in man (1), this source of supply would offer a significant amount. Third, it may be suggested that the modern method of agriculture tends to rob the land of iodine without any means of replenishing the supply. This is brought about by the constant use of the soil, the plants taking up the available iodine. The greater ease of fresh water perfusion in cultivated land is also a factor. Studies made in Germany (22) show an increased amount of goitre during the war, which is in part explained as due to the discontinuation of nitrates, containing also iodides, shipped in from Chile and the substitution of guano for fertilization.

This survey shows a decided increase in incidence of goitre among the Indians. It would seem that the tendency of the Indian to adopt the habits of civilized life can not account for it. If this were the case, the whites of non-goitrous regions should show a higher incidence. The diet, however, deserves consideration. In the Northwest, for instance, the salmon is taking a smaller and smaller place in the diet of the aborigines. This scarcity of salmon for the Indians has already been the cause of much complaint and court action (23). The purified foods, including white salt, are becoming the larger part of the diet. Thus the Indian of this district is being placed under the same living conditions as the whites. He also is starting to show the same high incidence of goitre as found among the white people of this district. In other parts of the country the sea food factor is eliminated. However, the question of diet is not eliminated. The Indian of today has not the quantity of wild game which was previously consumed. The salt supply of these natives was often crude salt which in many localities contains iodides. It would seem, then, that the purified diet may be a factor concerning the increased incidence of goitre in other districts.

Two districts other than the Northwest show decided increases of goitre that deserve special note. Oklahoma shows an increase from .02 per thousand to 1.6 per thousand. This State has been the great gathering point for many Eastern tribes. Although a careful study of the conditions could not be made, it seems probable that a change in environmental factors would explain this increase. North Carolina has an incidence which

has increased about 8000 times during the interval between surveys. These conditions, likewise, could not be carefully studied. The entire results from the second survey were obtained from the Cherokee school situated at Ashford, North Carolina. This city is also in the heart of the East's greatest precipitation area as well as being in a mountainous country. Therefore the factors are present in this locality which would favor iodine depletion.

Utah, although partly in the arid region, shows a high incidence of goitre in both surveys. This State's average is accounted for by the high incidence found among the tribes located in the northeastern part of the State. This location has a moderate rainfall and also is a more mountainous district than the rest of the State. The tribes of southern Utah show practically no goitre.

While most of our evidence points to iodine deficiency, the second class of etiological agents, i. e., toxic products, seems to play its part. Investigations have indicated that changes occur in the thyroid tissue following the administration of fecal substances (26). Such data would suggest an increased demand made upon the thyroid during intoxications by such substances. Farrant (25) has shown that many intoxicating diseases cause an increased activity of the thyroid gland as demonstrated by hyperplasia of this gland. He has even classified diseases by the manner in which they affect the thyroid substance. Among the afflictions which cause this change in the gland is tuberculosis. The increasing prevalence of this latter disease among the Indians has long been shown (24). It is suggested that the body needs more iodine during such a strain upon the organism and leads to the assumption of an iodine balance in this gland. As McCarrison (19) has pointed out, an iodine sufficiency may become a deficiency if some extra load is thrown upon the gland.

SUMMARY

1. Goitre is present among the Indians and the incidence of distribution is, for the most part, parallel to the distribution among the white population.

2. The greatest exception is noticed in the Pacific Northwest, where the natural Indian diet contains more iodine (salmon) than does the white man's diet.

3. Goitre is increasing among the Indians and this increase seems to be explainable by two factors, iodine deficiency and toxic influences upon the organism.

4. Simple goitre seems to be the result of iodine deficiency, produced by a low amount of iodine or an increased thyroid demand.

5. These results seem to offer further support of the work by Marine and co-workers (1) and McClendon (7).

BIBLIOGRAPHY

1. Marine, D., Lenhart, C. H., Kimball, O. P., Rogoff, J. M.: Compiled by G. N. Stewart. Western Reserve Univ. Pub., May 7, 1923.
2. McCarrison: The thyroid gland in health and disease. Wm. Wood & Co., N. Y., 1917.
3. Burget, C. E.: Am. J. Physiol. (Balt.), 1917, **44**, 492.
4. Watson, C.: J. Physiol. (Lond.), 1906, **34**, 111.
5. Bensley, R. R.: Anat. Record (Phila.), 1914, **8**, 431.
6. Forbes & Beegle: Bull. 299 Ohio Agr. Exper. Sta., 1916.
7. McClendon, J. F.: J. Am. M. Ass. (Chicago), 1923, **80**, 600.
8. McClendon, J. F.: Science (N. Y.), 1922, **56**, 269.
9. Kimball, O. P.: U. S. P. H. R., 1923, **38**, 877.
10. U. S. War Dept.: Defects found in drafted men. 1920.
11. Hart & Steinach: J. Biol. Chem. (Balt.), 1917, **3**, 313.
12. Bull. 30 Bur. Am. Ethnology. Handbook Am. Indians.
13. Hrdlicka: Bull. 34, 1908, Bur. Am. Ethnology.
14. Hayhurst, E. R.: J. Am. M. Ass. (Chicago), 1922, **78**, 18.
15. Blackmore: Chem. Abst. (Easton), 1912, **6**, 2055.
16. Phalen, W. C.: Bull. 669 U. S. Geological Survey Salt Resources of U. S.
17. Chamberlain & Salisbury: College textbook of geology. Henry Holt & Co., N. Y., 1909.
18. U. S. Dept. Agr., Weather Bureau, Henry, A. J.: Bull. Q, Climatology of the U. S. 1906.
19. McCarrison: J. Am. M. Ass. (Chicago), 1923, **81**, 1725.
20. Jordon, D. S.: Fishes. Henry Holt & Co., N. Y., 1907, 299-300.
21. Cameron: J. Biol. Chem. (Balt.), 1914, **18**, 335. Ibid., 1915, **23**, 1.
22. Bleyer: München. med. Wchnschr., 1922, **69**, 587-589; this Journal, 1922, **6**, 726.
23. Communication from Indian Service.
24. Report of Committee of Nat. Tuberc. Ass., appointed Oct. 28, 1921, on tuberculosis among the North American Indians. U. S. Indian Affairs Office. General Pub., 1923.
25. Farrant: Lancet (Lond.), 1913, **II**, 1820. Brit. M. J. (Lond.), 1914, **1**, 470.
26. Rush & Jones: Unpublished work. Univ. Ore. Dept. of Physiology.

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT*

By H. LISSER, M.D., and H. C. SHEPARDSON, M.D.

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It is unnecessary for the purposes of this brief paper to sketch the historical aspects of our knowledge regarding the pathogenesis of tetany. That tetany invariably follows removal of the parathyroid glands has been abundantly confirmed. Furthermore, many years have elapsed since MacCallum and Voegtlin demonstrated a low blood calcium content during attacks of tetany and showed that such attacks could be controlled or ameliorated by the intravenous injection of calcium. Inasmuch as severe parathyroid deficiency causes tetany, and since a striking diminution in the calcium content of the blood is always found under such circumstances, it seems altogether likely that calcium metabolism is, to some extent at least, regulated by parathyroid function.

Attempts to substitute for lack of parathyroid hormone in cases of tetania parathyreopriva, by administration of variously prepared parathyroid extracts, have been unsuccessful, the explanation for failure being the logical assumption that the preparations were inert and did not contain an active parathyroid hormone.

Late in 1924, J. B. Collip, Professor of Biochemistry at the University of Alberta, Canada, announced "the extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium." Thus another hormone of unquestionable potency was added to the list of thyroxin, insulin, pituitrin and adrenalin. Space forbids an adequate review of the elaborate and painstaking experiments on normal and parathyroidectomized dogs to whom this extract was administered; and the reader is referred to the articles by Collip and coworkers (1, 2, 4) which have appeared in The Journal of Biological Chemistry (1925). Suffice it to state

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that a stable and purified extract was prepared which, when injected subcutaneously, produced a rise in the blood calcium level, and which in overdosage produced an alarming and usually fatal hypercalcemia. It was furthermore shown that frequently repeated small doses of this extract are cumulative in action and will eventually raise the blood calcium to dangerous levels (values over 15 mg.), due to a "pyramiding of the effect of each successive injection upon the preceding one." Hence the importance of accurate and dependable blood calcium determinations to control the dosage, very much as one checks the administration of insulin by blood sugar estimations, and watches the effect of thyroid extract by determinations of the basal metabolic rate.

Eli Lilly and Company, in collaboration with Professor Collip, have prepared this parathyroid extract for clinical use.* The extract is standardized by its capacity to increase the total blood-serum calcium in normal dogs; and one unit is defined as one-hundredth the amount of extract required to cause an increase of 5 mg. of calcium in the blood-serum of a 20 kilogram dog, the rise of calcium being determined fifteen hours following the injection of the extract.

Tetania parathyreopriva is a comparatively rare experience nowadays since surgeons have learned to avoid the parathyroid glands in subtotal thyroidectomies. The complication may, nevertheless, occur even in the hands of skillful and experienced goiter surgeons, especially in the removal of large goiters adherent to the trachea and with substernal extension. It so happened that the appearance of symptoms of tetany in a patient, following thyroidectomy, provided us with the opportunity of administering Collip's parathyroid extract, to which the surgeon kindly consented, and which we were able to control accurately by repeated blood calcium determination. The laboratory, under the direction of Dr. Langstroth, used the Collip modification of the Kramer-Tisdall method (3) for estimation of blood serum calcium. Every precaution was used in the preparation of the syringes, needles, test tubes and apparatus to eliminate errors from calcium present in tap water. Many

*By the time this note is published, the extract will be available under the trade name "Para-thor-mone." The courtesy of Professor Collip and Eli Lilly and Company in presenting the writers with a generous supply of this extract for clinical trial is herewith duly acknowledged and appreciated.

of the specimens were checked in two different laboratories to insure accuracy.

We are aware of the fact that others in the United States and elsewhere have had an opportunity of trying this extract but we have as yet found only three reports of its clinical use.

Collip and Leitch (5) (January, 1925) report the first case of tetany to receive treatment with parathyrin. A girl 22 months of age, who weighed only 15 pounds and 12 ounces and suffered from a pronounced case of rickets, became feverish suddenly, vomited, breathed very rapidly (60 to the minute) and showed marked carpopedal spasm, hyperactive reflexes, and Chvostek's phenomenon. During the first two days, three doses of 1 cc. of Collip's parathyroid extract were given hypodermically. Improvement was so prompt and satisfactory that for the following four days 1 cc. of the extract was given by mouth twice daily, and finally for ten days 1 cc. by mouth daily. At the time of writing, one week had elapsed since the last dose of extract and no further evidence of tetany had developed.

In the course of an article on "Surgery of the Glands of Internal Secretion," Crile (6) writes as follows: "During the past six weeks we have been using the hormone discovered by Dr. J. B. Collip of Alberta University and have secured as definite results as he secured with his experimental animals in both acute and chronic cases of tetany. Five acute cases have been treated with relief in every case. Relief of symptoms is usually experienced within twenty minutes to one-half hour after the intravenous injection of 1 cc. of the hormone. In one exceedingly acute case, in which not a single one of the classical symptoms of tetany was lacking, the first dose was followed within twenty minutes by a disappearance of the subjective symptoms. Three doses of 2 cc. each resulted in complete recovery. Among the chronic cases treated, relief has been secured in about 85 to 90 per cent."

Davidson (7) (August, 1925) reports "a case of adolescent myxedema, accompanied by nephrosis and by tetany of parathyroid origin, treated with thyroid and Collip's parathyroid extract." A girl, aged 17 years, developed in December, 1922, a marked edema, followed by convulsions, there being some remission in summer of 1924, and marked recurrence in November,

Blood calcium was low. Under thyroid and calcium chloride the symptoms of myxedema almost disappeared and convulsions markedly diminished in number and severity. Commencing January 28, 1925, thyroid 6 grains daily, was continued, the calcium chloride discontinued, and daily injections of Collip's parathyroid extract begun, the dose being adjusted until the blood serum calcium remained constant between 10.9 and 11.5 mg. per 100 cc. The necessary dose for this was found to be at this period 2 to 4 cc. of the extract per day. On this treatment edema completely disappeared and the convulsions were controlled almost completely. This treatment was continued for two months, during which time the situation was complicated by influenza, otitis media, rubella and diphtheria. On April 1st she left the hospital and returned to her home in the country, and was without therapy for several weeks, but relapsed and on May 19th, on return to the hospital, was in a more critical condition than ever, but by the same treatment was restored to apparent normality within 14 days of readmission to the hospital. However, further infections developed and the patient finally died July 17th of severe toxemia of undetermined origin. Post-mortem examination revealed a very small atrophic thyroid gland and no parathyroids in either upper or lower normal positions; two were found in median positions, the left one somewhat atrophied and the right apparently normal. A chart includes percentage of albumen in the urine, several blood cholesterol and blood urea and basal metabolism determinations, and a great many blood serum calcium determinations together with the daily dose of parathyroid extract.

THE AUTHOR'S CASE

The patient, an obese woman 30 years of age, first visited the University of California Out-Patient Department in March, 1925, complaining of a goiter accompanied by mild dizziness, palpitation and nervousness. Her family history is unimportant, her father, mother and three sisters all being alive and well. She has been rather unfortunate in her marriages, her first husband having been a drug addict from whom she was divorced, without having been pregnant, four years after her marriage. Her second husband now has tuberculosis. There

are, however, three children living and well and she has had no other pregnancies. Libido is normal.

Her past history is interesting in that she lived only the first three years of her life in the northern part of California, a locality that is definitely a "goiter district." During the remaining twenty-seven years she has lived in or near San Francisco. She has been quite well educated and has been comparatively free from illnesses except for several attacks of tonsillitis which finally necessitated tonsillectomy when she was about 20 years of age.

She began menstruating at the age of 14 and her periods have been more or less irregular, the intermenstrual period varying from 14 to 40 days, averaging, however, approximately 28 days. The periods extend over from 1 to 3 days and are somewhat scant.

Soon after the onset of her menstrual function, she began to gain in weight. At the age of 15 her weight was about 130 pounds and she maintained this until her first child was born, at the age of 22. At that time the physician who attended her called her attention to the presence of a goiter. Following her delivery, she gained 70 pounds in one year (that is from 130 to 200 pounds). She weighed at the time of her first visit 225 pounds.

While she was somewhat vague about the onset of her symptoms (dizziness, nervousness and palpitation), she stated that they probably appeared sometime before the presence of the goiter, which was called to her attention at the age of 22. Their etiology is probably largely psychic, resulting from her unfortunate marriage to a narcotic addict at the early age of 15. As a matter of fact, when she separated from her husband some four years later, she had a mental upset which necessitated her remaining in bed for some six months, during most of which time she was irrational.

An interesting commentary on her disturbed metabolism is the fact that with each of her three pregnancies two teeth decayed completely.

Except for her marked adiposity, which had a tendency to be confined more or less to a girdle distribution, her physical examination disclosed no definite abnormalities except those

referable to her goiter, and there was but little evidence of toxicity. Her skin was somewhat moist; she had a slight tremor of the extended fingers and a blood pressure of 150/80. There were numerous large, soft, semifluctuant nodules easily palpable in the region of the thyroid gland. Her basal metabolic rate was 40.8% above the theoretical normal, but she did not cooperate well during the test.

Blood count was normal, as was the urine examination, except for the slightest possible trace of albumin in the voided specimen. Wassermann was negative. Roentgenological examination of the chest revealed a small substernal extension of the thyroid, causing some compression of the trachea.

In view of the fact that her goiter had recently been increasing in size and that there was evidence of beginning toxicity, surgical removal was advised, but the patient was unable to enter the hospital until several months later. On September 24, 1925, subtotal thyroidectomy was done under gas and oxygen anesthesia. The gland was found to be approximately ten times its normal size, extending posteriorly behind the trachea on both sides and with bilateral substernal extension. It was quite nodular and many small to medium sized adenomata could be palpated throughout the gland substance. These were removed and at the close of the dissection, minute portions of thyroid tissue remained over the trachea and in the region of the isthmus. The wound was closed without drainage and patient was returned to the ward in excellent condition.

On the evening of the second day, post-operative (September 26th), patient first noticed that the right thumb was drawn across the palm in spasm. From this time on she felt progressively more nervous and noticed muscle twitchings in various parts of her body, which gave her the sensation of "innumerable tiny quivering foci" in the muscles. Particularly did she notice almost a constant spasm of the muscles of the hands and feet. Two days later, these symptoms having constantly increased in severity and tetany being suspected, the writers were called in consultation.

Examination revealed a very apprehensive individual, nervous, frightened and in considerable pain from the various muscle spasms, especially of her hands and feet. Positive Chvostek

and Trousseau signs were easily elicited, Erb's phenomenon was markedly positive, the anodal opening contraction occurring with 3 milliamperes, the cathodal and anodal closing contraction occurring with 4 milliamperes when the right ulnar nerve was stimulated with galvanic current. In fact, she presented a classical picture of a moderately severe parathyroid insufficiency.

She had been given one gram of calcium lactate by mouth prior to this examination, and at 4 p. m. September 28th her blood serum calcium was 8.1 mg. per 100 cc. of blood. Treatment for the next three weeks was restricted to injections of a parathyroid extract, no calcium being administered and no modifications of the diet instituted. She was given 12½ units of parathyroid extract intramuscularly, but the following morning her fasting blood serum calcium was 7.6 mg. per 100 cc. of blood. On September 29th she received 25 units of parathyroid extract and subjectively felt much improved in spite of the fact that the fasting blood serum calcium on September 30th reached a low level of 7.2 mg. per 100 cc. The dosage of parathyroid extract was increased to 37.5 units on September 30th. On that day the Chvostek and Trousseau signs were still obtainable but much less marked than on the previous day and the patient stated that she "slept better the preceding night than she has for years." However, she did have some cramps in her feet during the night as well as occasional spasms of the epigastric muscles. On October 1st her fasting blood serum calcium had risen to 8.4 mg. per 100 cc.

Fluid had gradually collected in the wound and on October 1st, 35 cc. of serum were aspirated. On October 1st and 2nd, 37½ units of parathyroid extract were administered daily. The blood serum calcium remained at 8.4 mg. per 100 cc. but the patient improved subjectively. She had no more parasthesias, was no longer nervous or "jumpy" and during the night had only one leg cramp. Chvostek and Trousseau signs remained slightly positive. On October 3rd her fasting blood serum calcium was 8.7 mg. per 100 cc. and the parathyroid extract was reduced to 25 units daily. Her fasting blood serum calcium continued to rise, showing a cumulative action of the parathyroid extract, until on October 5th it reached 9.7 mg.

per 100 cc. The dosage of parathyroid extract was further reduced to 12½ units on October 5th and discontinued entirely October 6th. She was then completely free of symptoms, and Chvostek and Trousseau signs were not obtainable.

Coincidental with the discontinuing of the parathyroid extract, her fasting blood serum calcium began to drop. On October 6th it was 9.3 mg. per 100 cc. and on the 7th, 8.2 mg. per 100 cc. On the latter date the cathodal closing contraction occurred with 2.5 milliamperes while the cathodal opening contraction occurred with 3.5 milliamperes. Chvostek's sign was mildly positive and the patient complained of some superficial parasthesias over the forearms and a tendency for contractures of the middle, ring and little fingers. Her basal metabolic rate on this date was 13.8% above the theoretical normal, but she again failed to co-operate well. She was given 12½ units of parathyroid extract on October 7th and her blood serum calcium promptly rose to 10.7 mg. per 100 cc.

On October 8th, 35 cc. of serum was again aspirated from the wound and *no parathyroid extract was given.* Her fasting blood serum calcium immediately began to drop and continued to do so in spite of the administration of 5 units of parathyroid extract on October 10th and again on October 12th, reaching a low level of 7.4 mg. per 100 cc. on October 13th. Her general condition was good, no apprehension or other symptoms were present, but Chvostek and Trousseau signs were markedly positive. For some unexplained reason the electrical reactions obtained on October 13th were practically normal, the cathodal closing contraction occurring with 3.5 milliamperes and the cathodal opening contraction occurring with 7.0 milliamperes.

On October 13th she was given 25 units of parathyroid extract. The following day 10 units were given and on October 15th 10 units more were given. On October 16th Chvostek and Trousseau's signs could not be elicited and patient felt perfectly normal. The cathodal closing contraction occurred with 6 milliamperes and the cathodal opening contraction with 7 milliamperes. The fasting blood serum calcium, however, was still low—8.1 mg. per 100 cc. Because of the low blood serum calcium, 25 units of parathyroid extract were administered on October 16th, 17th and 18th. Her blood serum calcium on

October 19th rose only slightly to 8.2 mg. per 100 cc. As a result of this continued low fasting blood serum calcium, 50 units were administered on October 19th, 25 units being given about noon and 25 units about 9 p. m. On October 20th patient complained of listlessness, lack of energy, and preferred to remain in bed. Her fasting blood serum calcium was taken at 9 a. m. and found to be 10.5 mg. per 100 cc. The administration of extract was therefore discontinued and on October 21st the fasting blood serum calcium had risen even higher, it being 11.9 mg. per 100 cc.

After reaching this high level, the calcium content of the blood serum began to drop. On October 23rd it reached 8.4 mg. per 100 cc. Calcium lactate by mouth was then given, no parathyroid extract being administered. On October 23rd, 24th and 25th patient received 3 grams daily. The morning of October 26th her fasting blood serum calcium had again reached the low mark of 7.2 mg. per 100 cc. On October 26th the calcium lactate was increased to 8 grams and on October 27th she received 12 grams. However, the following day her fasting blood serum calcium was only 8.4 mg. per 100 cc.

It became evident that it would probably be impossible to force her blood serum calcium to normal by means of the oral administration of calcium lactate alone, and in view of the fact that the patient was again having symptoms, such as cramps in her feet and arms together with some parasthesias, her calcium lactate was, on October 29th, reduced to 5 grams daily and she was given 10 units of parathyroid extract every other day and kept on a general diet.

She was discharged from the hospital on October 30th because of the necessity of her returning to her family. She was carefully instructed in the hypodermic administration of the parathyroid extract, of which she will give herself 10 units every other day. In addition, she will continue to take calcium lactate by mouth, 5 grams daily in divided doses. Her fasting blood serum calcium on November 2nd was 8.9 mg. per 100 cc. and it will be checked once a week and oftener if necessity requires.*

*Blood serum calcium Nov. 6 was 8.8 mg. per 100 cc. Beginning Nov. 9, she will give herself injections of 10 units of parathyroid extract daily instead of every other day. She is free from symptoms.

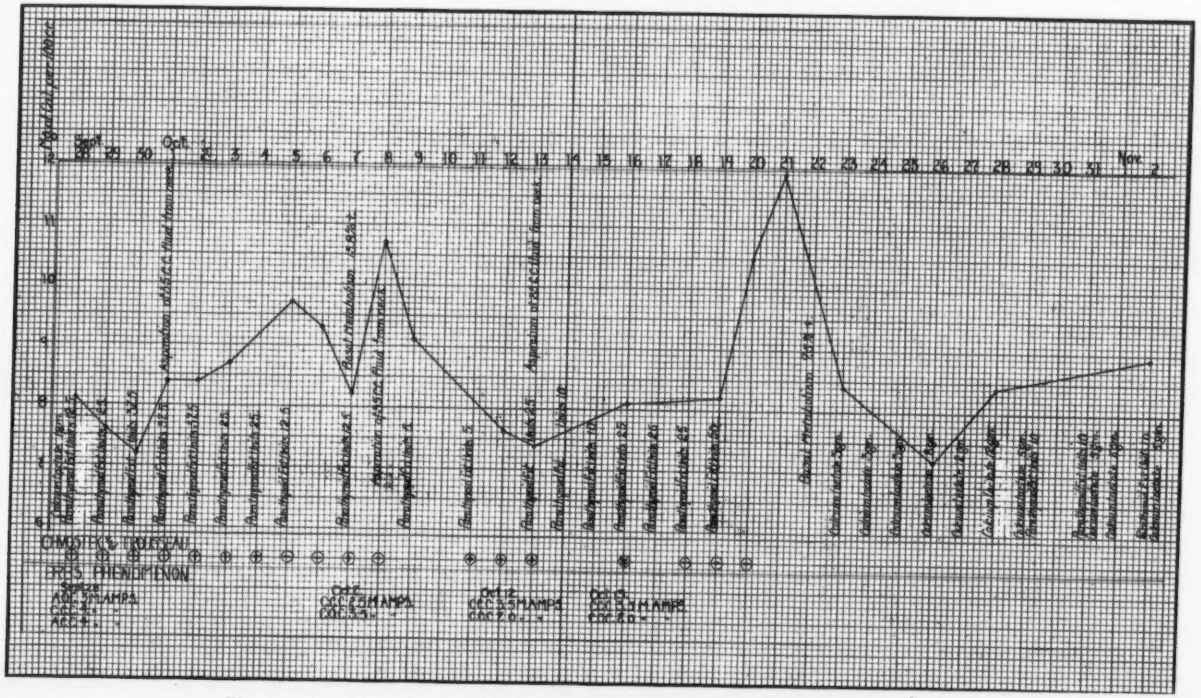

Fig. 1. Chart of treatment administered, blood serum calcium response and reflex reactions.

The accompanying chart summarizes the above description, and illustrates the response of the fasting blood serum calcium to injections of Collip's parathyroid extract. The status of nervous excitability is also recorded by the presence or absence of Chvostek's and Trousseau's phenomena.

For the first few weeks following operation there was some question as to whether the tetany arose from interference with the blood supply of the parathyroid glands, or was due to their accidental removal. This doubt was finally settled when careful search of all the tissue removed disclosed the presence of three separate parathyroid glands. This conclusively established the diagnosis of tetania parathyreopriva.

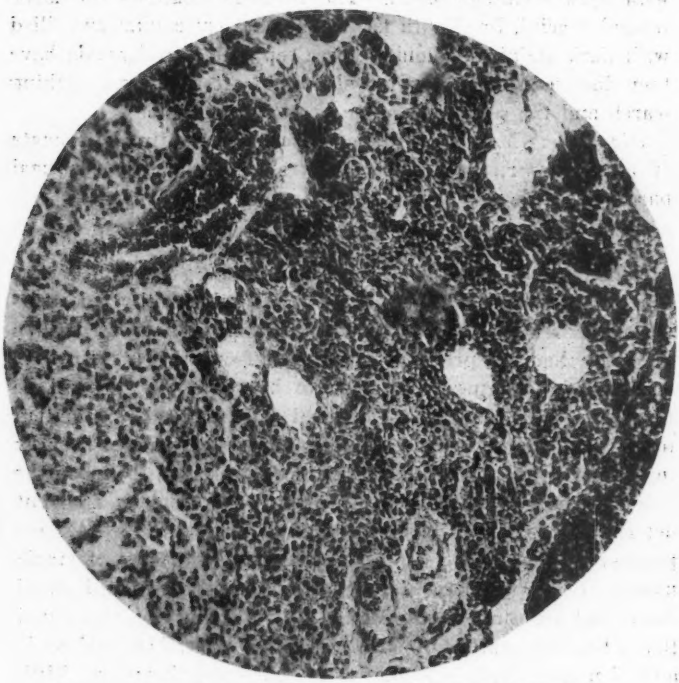

Fig. 2. Section of parathyroid tissue found in removed specimen.

Gross Pathology: Specimen is two masses of tissue measuring 11x6x4 cm., weighing 235 grams. The anterior surfaces are encapsulated and nodular and the posterior show the rough

plane of resection. Cut surface shows multiple nodules, the largest 3.5 cm. in diameter, and their contents are degenerating colloid.

Multiple large and small degenerating adenoma of adult pattern in a thyroid gland.

Microscopic Pathology: Section shows closely packed adenomata. Small pieces of compressed gland proper are made up of small regular acini lined with flat epithelium and filled with dark staining colloid. The adenoma contents are large irregular acini, lined with flat to cuboidal epithelium and filled with dark staining colloid. Three separate parathyroids have been discovered. They were only found after very painstaking search and the sectioning of many blocks of tissue.

Diagnosis: Multiple large and small degenerating adenomata of adult pattern in a normal thyroid gland. Three normal parathyroid glands.

DISCUSSION

The case reported above is the first detailed record of tetany in a human being resulting from accidental parathyroid extirpation, in which Collip's parathyroid extract was used. We therefore had no previous experience from the literature to guide us in judging the dosage to be employed. It will be remembered that in Collip's original article he called attention to the fatal hypercalcemia which could be produced in dogs by injections of his extract. We therefore preferred to err on the side of conservative dosage, controlling the same by frequent determinations of the blood serum calcium. Collip's later experiments in which he contrasted the relative safety of single massive doses with the danger of frequently repeated small doses, had not come to our notice. In reporting these he stated that a long maintained hypercalcemia was invariably fatal while a sudden brief hypercalcemia was comparatively harmless. With this in mind it is interesting to observe that the two high peaks of blood serum calcium reached on October 8th and 21st, resulted from the cumulative effect of injections administered daily over a period of several days. Fearing a further rise of the blood serum calcium to dangerous levels, the administration of the extract was immediately discontinued on both occasions. That the effect of the dosages we employed was transitory is

shown by the fact that in each case five days later the blood serum calcium had dropped to the original low level of 7.2 mg. to 7.4 mg. per 100 cc. It is also interesting to observe that when the parathyroid extract was discontinued the second time, the blood serum calcium continued to fall despite the oral administration of ordinary doses of calcium lactate and was only slightly elevated later by fairly large doses.

Before we were certain that parathyroid tissue had actually been removed and while there was a reasonable possibility of the tetany being due to pressure ischemia from the collection of fluid in the wound, it was thought that possibly the first rise in blood serum calcium might be due to the aspiration of 35 cc. of serum rather than to the parathyroid extract injected. This assumption was shown to be false when a second aspiration of a similar amount of fluid eight days later at a time when parathyroid extract was withheld was accompanied by a fall rather than a rise of the blood serum calcium.

In our observation of this case, we were struck by the fact that subjective improvement was almost immediately effected by the parathyroid extract, and preceded by several days the objective improvement as evidenced by the reaction to Chvostek's and Trousseau's maneuvers, and that relief of symptoms occurred considerably in advance of any marked elevation of the blood serum calcium.

Collip states that the first definite symptom of parathyroid hormone overdosage observed in dogs was vomiting. We never pushed the blood serum calcium high enough in this patient to produce this symptom, but it is perhaps worth recording that when the blood serum calcium reached 11.9 mg. per 100 cc. she complained of listlessness and lack of energy and preferred to remain in bed, which was in sharp contrast to her feeling of well being on the previous few days.

It is perhaps premature at this writing to forecast the future of this patient, but it would seem likely that she can be kept free from symptoms and her blood serum calcium maintained at a normal level by the injection of small doses of parathyroid extract combined with calcium lactate by mouth.

In view of the fact that at least three parathyroid glands were inadvertently removed, it is altogether probable that treat-

ment will have to be continued more or less indefinitely. This is in accordance with the necessity for life-long administration of thyroid extract in pronounced myxedema. If this individual still possesses one parathyroid gland, compensatory hypertrophy may gradually ensue and eventually produce sufficient hormone to maintain a normal blood serum calcium. The authors hope to keep in touch with this patient and render a further report after long continued observation.

SUMMARY

1. A woman, 30 years old, was operated upon for a large adenomatous goiter. The mass extended under the sternum and posteriorly behind the trachea.

2. Three parathyroid glands were accidentally removed. The status of the fourth parathyroid gland is unknown.

3. The patient promptly developed tetania parathyreopriva.

4. A detailed account of the treatment with Collip's parathyroid extract together with its effect on the blood serum calcium is given in the text and summarized in a chart.

5. No calcium was administered during the first three weeks except for one gram of calcium lactate by mouth prior to beginning of parathyroid injections, and the patient was kept on a regular ward diet.

6. The effect of the parathyroid extract on the subjective symptoms, objective findings and blood serum calcium, is discussed.

7. This new parathyroid hormone seems to be a true specific for parathyroid tetany.

BIBLIOGRAPHY

1. Collip, J. B.: The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium. Jr. Biol. Chem., 1925, **63**, 395-438.
2. Collip, J. B., Clark, E. P., and Scott, J. W.: The effect of a parathyroid hormone on normal animals. Jr. Biol. Chem., 1925, **63**, 439-460
3. Clark, E. P., and Collip, J. B.: A study of the Tisdall method for the determination of blood serum calcium with a suggested modification. Jr. Biol. Chem., 1925, **63**, 461-464.
4. Collip, J. B., and Clark, E. P.: Further studies on the physiological action of a parathyroid hormone. Jr. Biol. Chem., 1925, **64**, 485-507.
5. Collip, J. B., and Leitch, D. B.: A case of tetany treated with parathyrin. Canad. M. A. J., 1925, **15**, 59-60.
6. Crile, G. W.: Surgery of the glands of internal secretion. Endocrinology, 1925, **9**, 301-309.
7. Davidson, J. R.: A case of adolescent myxoedema, accompanied by nephrosis and by tetany of parathyroid origin, treated with thyroid and Collip's parathyroid extract. Canad. M. A. J., 1925, **15**, 803-808.

HYPOPITUITARISM AND DIABETES

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Anatomically the hypophysis cerebri is divided into three portions, the pars anterior, the pars intermedia and the pars posterior. Clinically, however, the pars intermedia and the pars posterior can not well be separated, as the extract of the pars posterior also contains that of the pars intermedia. The hormone of the pars anterior affects chiefly the osseous and the genital systems, hypersecretion producing gigantism early in life and acromegaly after growth has ceased, with secondary effects on the dermal system, temperature, pulse, blood pressure and mental function. The hormone of the pars posterior chiefly affects metabolism; hyposecretion produces increased carbohydrate tolerance and adiposity; hypersecretion, decreased carbohydrate tolerance with polyuria; it also causes contraction of the unstriped muscle.

I am interested chiefly in the relation of carbohydrate metabolism to variations in pituitary activity and therefore shall deal merely with this phase of the subject.

Engelbach (1) found that hyposecretion of the posterior lobe produced increased carbohydrate tolerance in 91.4 per cent of his cases and a decrease in 8.6 per cent. This is the general conclusion of most authors. But Engelbach found also that hyposecretion of the anterior lobe produced increased carbohydrate tolerance in 71.5 per cent of his cases and a decreased tolerance in 28.5 per cent. (See Table I.) It would appear therefore that the carbohydrate tolerance does not provide a definite criterion whereby to differentiate the functional ability of either of these two lobes of the pituitary gland.

Sachs and Macdonald (2) have found that in animals after the removal of the pituitary gland the fasting blood sugar was slightly lowered and a transient glycosuria which they consider of no importance followed the operation. When they removed

TABLE I

Glucose Tolerance in Pituitary Disease
(after Engelbach)

	Hypopituitarism Ant. Lobe	Hypopituitarism Post. Lobe	Hyperpituitarism Ant. Lobe	Hyperpituitarism Post. Lobe
Tolerance increased in.....	71.5%	91.4%	66.6%	66.6%
Tolerance decreased in.....	28.5%	8.6%	33.3%	33.3%

Anterior lobe dyscrasia, 10 cases—
Decreased carbohydrate tolerance in 7 or 70 per cent.
Increased carbohydrate tolerance in 3 or 30 per cent.
Hypopituitarism (anterior lobe), 7 cases—
Decreased carbohydrate tolerance in 2 or 28.5 per cent.
Increased carbohydrate tolerance in 5 or 71.5 per cent.
Hyperpituitarism (anterior lobe), 3 cases—
Decreased carbohydrate tolerance in 1 or 33.3 per cent.
Increased carbohydrate tolerance in 2 or 66.6 per cent.
Hyperpituitarism (posterior lobe)—3 cases—
Decreased carbohydrate tolerance in 1 or 33.3 per cent.
Increased carbohydrate tolerance in 2 or 66.6 per cent.
Hypopituitarism (posterior lobe), 58 cases—
Decreased carbohydrate tolerance in 5 or 8.6 per cent.
Increased carbohydrate tolerance in 53 or 91.4 per cent.

merely the anterior lobe the blood sugar was normal. They were unable to produce a permanent glycosuria experimentally. In all of these animals except those in which only the anterior lobe has been removed, the highest rise in the blood sugar curve was at the end of one hour, which suggests a lessened tolerance in contrast to the curve in normal animals in which the highest rise occurs at the end of one-half hour.

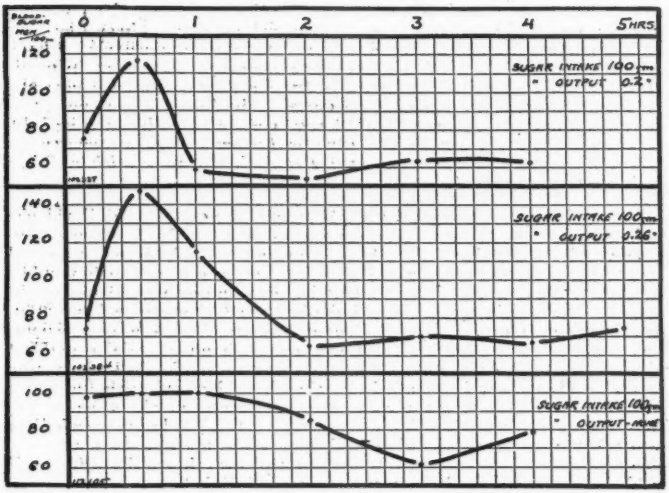
The data that I have been able to gather from the records of the Cleveland Clinic are as follows:

Total number of cases of pituitary disease—41.
Hypopituitarism, 31—
Without glycosuria, 26 or 83.8 per cent.
With decreased carbohydrate tolerance, including diabetes, 5 or 16 per cent.
Acromegaly, 7—
Without glycosuria, 4 or 57.1 per cent.
With glycosuria, 3 or 42.8 per cent.
With diabetes, 2 or 28.8 per cent.

As has been stated above, hypopituitarism suggests increased carbohydrate tolerance. That this rule does not hold invariably, however, is shown by Chart I, which shows the glucose tolerance curves secured in three cases of hypopituitarism, each of

which had the typical clinical symptoms of the disorder. The first (upper curve) of these patients was a man 51 years of age with typical voice changes, impotence for 5 years and lack of mental alertness. The x-ray plate showed the sella to be normal. The second case (middle curve) was a boy 22 years of age, who

CHART I



Glucose tolerance in cases of hypopituitarism

looked like a lad of 12 or 14 years. He had a high-pitched voice, undeveloped genitalia and was mentally dull. The x-ray plate of the sella showed no enlargement. The basal metabolism was minus 17.7 per cent. The third case (lower curve) was a man 36 years of age with diminished energy. He had lost most of the hair from all parts of the body, and was quite nervous; the genitalia were normal. Two of these patients showed a slight postprandial glycosuria, the renal threshold for sugar being apparently quite low in both. There was no glycosuria in the third case. The upper and lower curves are of the type which denotes increased carbohydrate tolerance. On the other hand, the second curve is a type which we get in normal individuals, and yet this patient had the most typical case of hypopituitarism in this group, showing all the signs of pituitary dysfunction.

Moreover, that an individual with hypopituitarism is not free from the disorder that is the most typical of a decreased carbohydrate tolerance, viz., diabetes, can be seen by the following cases.

Case I. A married woman 27 years of age. She had had no illnesses excepting tonsillitis and influenza. When I first saw her the menses were regular but scanty, but they ceased shortly afterwards (14 months ago); and adiposity has developed during the past few months, her weight rising from 125 to 205 pounds. There has been no disturbance in vision. She drinks and urinates excessively. Physical examination disclosed nothing of importance except an infantile uterus. The x-ray plate of the sella turcica shows a normal size and contour. There has been no glycosuria. The blood Wasserman test was negative. Blood urea was 24 mg. per 100 cc.; blood creatinin, 1.05 mg. The findings in the glucose tolerance test as shown on Chart II, upper curve, gave a typically diabetic curve with a fairly high renal permeability.

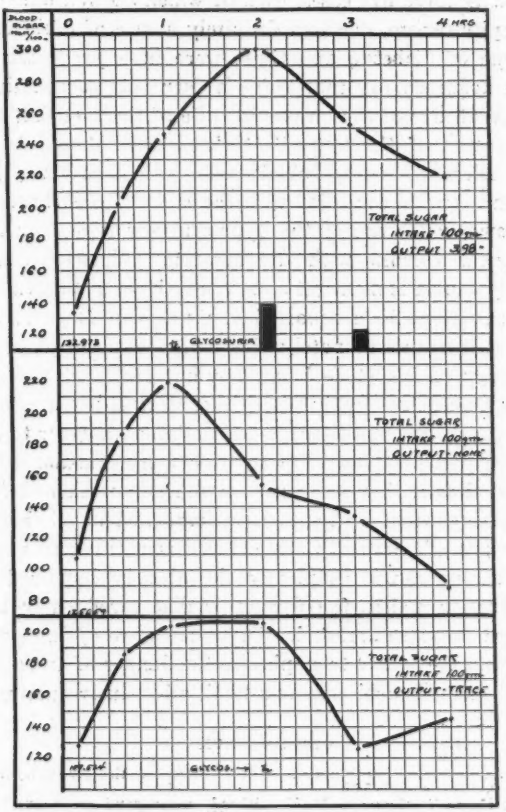
Case II. An unmarried girl, 18 years of age. In childhood she had had measles, mumps and chickenpox; later in life influenza, tonsillitis and rheumatism. Her tonsils and adenoids had been removed a year before. She complained of nervousness and stomach trouble. During the five months before I saw her she had gained 25 pounds in weight. Her hands were cold and she had marked perspiration. Menstruation was regular. Physical examination showed a very corpulent young woman weighing 214 pounds, with an especially marked adipose layer over the hips. The distribution of the body hair was normal. There was hyperplasia of the thyroid gland with increased vascularity. There was a slight systolic murmur at the apex of the heart; the pulse was 124; the blood pressure 128/60; basal metabolism minus 8 per cent. The radiograph showed a normal sella turcica. The findings in the glucose tolerance test as shown by Chart II, middle curve, suggest the presence of a mild diabetes.

Case III. A single woman, 32 years of age, of retarded mental development. There was no history of any previous disease. The patient reported that she had had sugar in the urine for the preceding two years. She was very fond of sweets, and had an enormous appetite. She sometimes had polyuria. She had some pruritus vulvae. She had lost no weight. She became stout and flabby after puberty. The menstrual periods were irregular. Physical examination showed an obese young woman 5 feet 6 inches in height, weighing 190 pounds. The blood pressure was 115/75. Her expression was rather listless, features were coarse, eyesight poor. The skin over the face and neck was very red. Her breasts were undeveloped. The distribution of pubic hair was of the male type. There was no glycosuria. The glucose tolerance test gave a record which showed that this was a borderline case of diabetes. (Chart II, lower curve.)

Case IV. A girl 11 years of age. Her only previous illness had been several attacks of tonsillitis. She came to the clinic because of headache and nervousness. Physical examination showed an obese little girl, weighing 120 pounds, of sluggish mentality, with no other abnormal physical findings. The x-ray plate showed the sella turcica to be slightly smaller than normal. There was no glycosuria. The glucose tolerance test showed a slight decrease in carbohydrate tolerance; that is, like the preceding case, this was a borderline case of diabetes.

Case V. A married woman, 25 years of age. There was no history of any childhood diseases but she had had pneumonia, grippe, tonsillitis and influenza. She complained of a continuous headache and pains in the back, of 8 years duration, always increased at the

CHART II



Glucose tolerance curves in cases of hypopituitarism, showing the presence of definite diabetes (upper curve), mild diabetes (middle curve) and prediabetic stage (lower curve).

menstrual periods. The menses were regular but she had severe dysmenorrhoea. During the preceding year she had gained 20 pounds and 40 pounds the year before. Physical examination showed a very obese woman 5 feet 3 inches in height and weighing 200 pounds. There was marked hypertrichosis of the face and chest. The axillary hair was normal, the hair distribution on the pubis was

of the male type. The thyroid was enlarged. The heart was normal, the blood pressure 126/86. The x-ray plate showed the sella turcica to be enlarged. The blood Wassermann test was negative. The blood urea was 15 and uric acid 4 mg. per 100 cc. There was no glycosuria. The glucose tolerance test suggested a decreased carbohydrate tolerance—a mild type of diabetes.

Among these five cases, each of which showed clinical signs of hypopituitarism, one was definitely a case of diabetes, one a mild type of diabetes, and three were in a prediabetic stage. We can definitely say that there is decreased carbohydrate tolerance in all five of these cases in spite of the fact that theoretically, because of the hypopituitarism, there should be an increased tolerance for carbohydrates. Van Noorden (3) called attention to such a condition when he said: "Recently cases have been shown which are of the hypopituitary type (for instance hypophyseal tumors with degeneration adiposo-genitalis) in which glycosuria is manifest and even diabetes mellitus appears." The observations here reported confirm Van Noorden's statement, but they unfortunately give us no information regarding the etiology of diabetes—I can not but feel that the diabetes which is present in hypopituitary disorders is but a coincidence —and that the hypopituitarism has nothing whatever to do with it. These patients may be born with a hypoinsulogenic function; and thus if they happen to strain this weakened function by overeating, which seems to have happened in all these cases, for they are all markedly obese, there is nothing to stop them from breaking down completely the already impaired insulogenic function unless the danger is discovered early and the downward progress arrested. These cases are of interest, however, in that they serve to emphasize the danger of accepting any apparent physiological rule as a final, all-inclusive dictum.

BIBLIOGRAPHY

1. Engelbach, W.: Classification of disorders of the hypophysis. This Journal, 1920, 4, 347-365.
2. Sachs, E., & MacDonald, M. E.: Blood sugar studies in experimental pituitary and hypothalmic lesions, with a review of literature. Arch. Neurol. & Psychiat. (Chicago), 1925, 13, 335-368.
3. Van Noorden : Die Zuckerkrankheit und ihre Behandlung (Berlin), 1920, 7 ed., p. 99.

STUDIES ON VIGOR. VI. THE EFFECT OF STARVATION ON THE SPONTANEOUS ACTIVITY OF CASTRATED RATS

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In a previous report (Hoskins, 1925-a) it was shown that castration in rats results in a marked depression of spontaneous activity. Similar results have been obtained by Allen (1925) at the Phipps Psychiatric Clinic of the Johns Hopkins Hospital. An animal deprived of its testes at about the time of puberty manifests throughout what would otherwise have been its most vigorous period a degree of activity corresponding to that of the early senile phase.

Such observations lend plausibility to the theory that a part of the inactivity of old age is due primarily to lack of testicular hormone. Whether this inactivity is due merely to lack of some stimulating element or to secondary structural changes is by no means clear. The problem is under investigation in our laboratory. It is significant that castrated rats, like castrated farm animals, show no obvious decrease in actual strength, though adequate determination of endurance are lacking.

It is not improbable that deficiency of testicular hormone may play a significant role in clinical conditions marked by lack of vigorous initiative. While "hypogonadism" can not be excluded from the endocrine phantasmagoria, neither can it definitely be included. Although there is no respectable basis for dosing patients with dried testicle, the subject of clinical gonad deficiency is a proper one for careful study.

In connection with investigations of the effects of castration, various attempts have been made toward ameliorating the characteristic depression. An initial study of testicle grafting gave completely negative results (Hoskins, 1925-b). These studies are being continued in the hope that a more adequate technic may be evolved and give positive effects.

It was thought that the castration depression might involve a vicious circle: that the inactivity would lead to partial clogging of active body tissues with fat, which condition in turn would tend to augment the inactivity. If this were true a period of starvation might be followed by a phase of augmented vigor such as Carlson has reported in man (1914). It was believed that greater activity would in all probability result during the period of fasting, if for no other reason, because the gastric hunger contractions would serve as a continuously acting stimulus. Powelson (1925) has shown by direct observation in this laboratory that there is a considerable degree of correlation in the rat between gastric peristalsis and spontaneous movements.

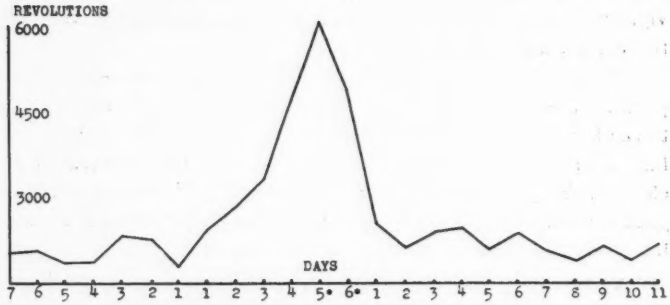

Fig. 1. Activity of starved castrated rats as manifested by turning revolving cages one foot in diameter; 7 days' preliminary period, 6 days inanition period, and 11 days post-inanition period on full diet. Averages for fifth and sixth days based on six animals, only.

In the experiments herein reported ten castrated rats ranging in age from 221 to about 450 days were subjected to starvation, six for six-day periods and four for four days. They were continuously supplied with water. Their spontaneous activity was determined by the revolving cage method used in previous researches (Durrant, 1924, 1925; Hoskins, 1925).

For a week previous to the starvation period the average cage activity of the group, as shown in the accompanying table and figure, ranged from approximately 1,744 to 2,280 yards daily. During the starvation period the activity reached approximately three times that of the initial period. In two of the six animals starved for six days the maximum activity was

Animal No.	DAYS BEFORE STARVATION							STARVATION PERIOD—DAYS						DAYS AFTER STARVATION									
	7	6	5	4	3	2	1	1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11
114	1620	780	1690	730	1760	720	1570	1450	3220	3500	5490	7820	6070	4350	3690	1810	2850	2780	2950	2660	2460	3700	1880	2890
148	2690	2650	1650	3100	2560	6050	1640	4680	3660	6540	8170	10060	6610	4530	2610	7020	4110	2810	4680	4090	1890	1880	3170	4160
159	730	1150	850	550	780	770	1120	1540	1990	2280	3121	5600	3540	2160	2810	3200	2730	3070	2300	1930	1560	2770	2670	1480
216	940	1150	1710	570	1190	1360	1410	1640	2650	2890	5100	5580	5810	1680	2400	2470	2830	2700	2130	1680	1220	2740	2560	1930
273	1460	770	870	1110	1050	810	1080	1320	1530	2500	3270	3020	2360	1730	20	10	0	10	80	150	150	130	420	20
280	620	880	750	1170	790	760	900	1160	1310	1520	2350	4410	4930	2150	1220	1350	1610	2010	1030	900	1630	1820	580	720
10	1870	2350	1640	1300	3770	1540	1820	1600	1540	1950	3620	.....	.....	760	1140	530	1500	1020	2990	1680	500	760	1250	1250
175	4450	5080	4270	3830	5080	4040	3760	4680	3910	2220	5340	.....	.....	2710	2570	1580	2660	1850	2330	1990	2600	2600	1820	2770
181	3050	3210	3160	4470	4010	3620	2680	3500	5230	6440	6690	.....	.....	3080	3290	3070	4220	2870	2740	3640	4720	3280	2020	4620
197	2630	2390	1650	1420	1810	2800	1460	2340	2930	3400	3820	.....	.....	2270	1880	2170	1890	1920	2000	1690	1750	1810	2290	1790
Average	2006	2041	1824	1825	2280	2247	1744	2391	2797	3304	4697	6082	4887	2542	2163	2321	2440	2104	2323	2041	1848	2149	1866	2163

recorded on the sixth day; in three, on the fifth day, and in one, on the fourth day. In case of those starved four days only the maximum activity in each case occurred on the fourth day. The activity was tabulated for a period of eleven days after the animals were returned to full rations.* The average activity of the whole group returned almost to normal on the second day after feeding was resumed. A study of the individual records, however, indicates that this average serves to mask two opposite tendencies. In four cases the activity level was considerably higher for several days than during the initial period. In three other cases it was as definitely lowered. In the latter cases it is probable that the starvation was carried to a physically detrimental length. Indeed, in case of four normal control animals similarly subjected to inanition death resulted on the third or fifth days.

A further study with detailed observations on weight loss and recovery is in progress.

SUMMARY

Ten castrated rats were subjected to four or six days' starvation. Their spontaneous activity as registered by the revolving cage method was augmented about 200 per cent. In four cases the increased activity persisted for several days after full feeding was resumed, whereas in three a depression, probably due to resulting physical debility, ensued.

BIBLIOGRAPHY

Allen, F. H.: 1925. Personal communication.
Carlson, A. J.: 1914. Am. J. Physiol. (Balt.), **33**, 95.
Durrant, E. P.: 1924. Am. J. Physiol. (Balt.), **70**, 344.
1925. This Journal, **9**, 221.
Hoskins, R. G.: 1925. (a) Am. J. Physiol. (Balt.), **72**, 324.
1925. (b) This Journal, **9**, 277.
Powelson, M. H.: 1925. Science, **62**, 247.

* Our stock ration consists of whole wheat flour, 62.5%; casein, 15%; skim milk powder, 15%; $CaCO_3$, 1.5%; NaCl, 1%; oil or fat, 5%; with addition of cod liver oil, fresh cabbage and corn.

A NOTE ON THE EFFECT OF ADRENALIN UPON STRIPS OF EXCISED PREGNANT HUMAN UTERUS

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ST. LOUIS

A large number of studies (1) have been performed to determine the excitability of excised strips of pregnant and non-pregnant human uteri. To Rübsamen and Kligermann (2) credit should be given for having been the first to observe the effect of suprarenalin upon excised strips of both gravid and non-gravid human uteri. They noted suprarenalin to produce contraction or increased tonus in both types. Two years later, without apparent knowledge of previous work having been done upon the human uterus, Gunn (3) studied the effect of adrenin upon strips of excised uteri of rabbits, cats and guinea pigs. He also studied the effect of this drug in four strips of excised human Fallopian tubes and in one instance upon the uterus. He found adrenine to produce contraction, i. e., increased tonus, in both organs and therefore concludes "unless, however, the human uterus has a still different type of sympathetic innervation from that of all the animals which have been examined, the probability is that adrenine will have a motor effect on the pregnant human uterus, and that, therefore, the use of sympathomimetic substances in labor is justified."

In 1915 Lieb (4) reported the effect of epinephrine upon a strip of excised non-gravid human uterus and its effect upon strips of "parturent" human Fallopian tubes. From these experimental observations he believes the conclusion to be justified that the sympathetic innervation of the human uterus is always motor in quality.

Because of these latter conclusions an attempt was made to confirm if possible Rübsamen and Kligermann's (2) results upon excised normal gravid human uteri.

*For this material the author is indebted to Dr. Otto Schwarz of the Department of Obstetrics, Washington University Medical School, whom he wishes to thank.

METHOD

The strips of uteri used were narrow sections cut from the walls of normal pregnant human uteri when Caesarian sections were performed in cases where there existed a disproportion in size of the fetus to the pelvic outlet.* Three such strips were studied. These strips were fresh and used shortly after removal. They were immersed in warm 38.5°C Locke's solution, through which a constant stream of oxygen flowed. The methods for recording, etc., were essentially the same as those used by Kehrer (1b). The time interval was thirty seconds. Adrenalin chloride (Parke Davis & Co.) was used. This was added directly to the fluid which bathed the muscle.

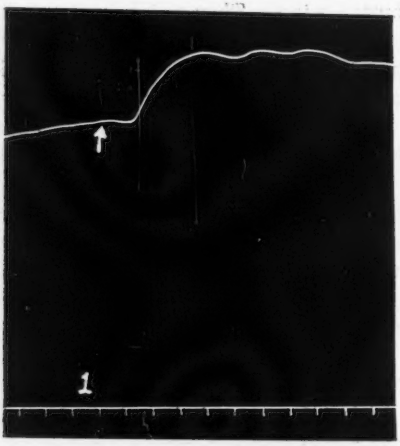

Figure 1. Excised strip of a normal pregnant uterus at term. The up stroke represents contraction, the down stroke relaxation. 1, adrenalin chloride was added to make a 1:200,000 solution bathing the tissue.

RESULTS

Our results on the effect of adrenalin on excised strips of pregnant human uteri confirm the finding of Rübsamen and Kligermann (2). In the three cases thus studied 0,5 ml. adrenalin chloride 1:1000 added to the Locke's solution, making a 1:200,000 adrenalin chloride dilution, caused a marked increase in the tonus of the pregnant uterus. Figure 1 is typical of the results obtained from all such uteri. In this and in the other

cases the increased tonus lasted for a long time. Weaker solutions appeared to have a similar effect though less in degree.

DISCUSSION

It has been demonstrated by Cannon and his coöperators (5) that the adrenal secretion is stimulated by pain, excitement, etc. Cannon and Gray (6) demonstrated decreased coagulation time of the blood after the injection of small doses of adrenalin. Similar results were obtained by Cannon and Mendenhall (7) upon stimulation of the splanchnic nerves with the adrenal glands intact and upon stimulation of the sciatic nerve (8). That adrenalin alleviates fatigued muscle was demonstrated by Cannon and Nice (9) and by Gruber (10). Upon the basis of these findings we may assume that if there is increased secretion of adrenalin during labor, it would produce increased tonus of the uterus, increased force of contraction of the abdominal muscles and decreased coagulation time of the blood during and after labor, and we agree with Gunn (3) that the use of sympathominetic substances in labor is justified.

SUMMARY

The effect of adrenalin was studied upon strips taken at the time of Caesarian section from three pregnant human uteri. In each case our results confirm the findings of previous investigators in that it increased the tonus of the muscle.

BIBLIOGRAPHY

1. (a) Franz: Ztschr. f. Geburtsh. u. Gynæk. (Stuttg.), 1904, **53**, 361.
   (b) Kehrer: Arch. f. Gynæk. (Berl.), 1907, **81**, 160.
   (c) Rübsamen & Danziger: Ztschr. f. Geburtsh. u. Gynæk. (Stuttg.), 1911, **69**, 656.
   (d) Rübsamen & Perlstein: Arch. f. Gynæk. (Berl.), 1912, **95**, 105.
2. Rübsamen & Kligermann: Ztschr. f. Geburtsh. u. Gynæk. (Stuttg.), 1912, **72**, 27; abst., Ztschr. f. Biochem. u. Biophys., 1912, **14**, 602.
3. Gunn: Proc. Roy. Soc., 1914, **B. 87**, 551.
4. Lieb: Am. J. Obst., 1915, **71**, 217.
5. (a) Cannon & de la Paz: Am. J. Physiol. (Balt.), 1911, **28**, 64.
   (b) Cannon & Hoskins: Ibid., **29**, 274.
   (c) Cannon: Ibid., 1914, **33**, 358; ibid., 1919, **50**, 399; etc.
6. Cannon & Gray: Ibid., 1914, **34**, 232.
7. Cannon & Mendenhall: Ibid., 243.
8. Cannon & Mendenhall: Ibid., 251.
9. Cannon & Nice: Ibid., 1913, **32**, 144.
10. Gruber: Ibid., 1914, **33**, 335; ibid., **34**, 89; ibid., 1917 **43**; 530; ibid., 1918, **45**, 302; ibid., 1922, **61**, 475; ibid., **62**, 438; etc.

STUDIES ON THE OESTROUS CYCLE IN THE RAT. I. THE EFFECT OF THYROIDECTOMY

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The thyroid gland has long been considered to have a rather intimate functional relationship with the female gonads. This opinion has been held largely on account of the swelling of the thyroid at puberty, menstruation, pregnancy and the menopause, and because of the fact that Graves' disease is more common in women than in men (Gley, 1917; Vincent, 1925). Up to the present definite experimental evidence establishing or refuting such a relationship has been lacking, due largely to the fact that we have had no adequate method of determining slight variations from normal ovarian function. Hammett's recent statistical study (1925) indicates that the assumed importance of the thyroid-ovarian relationship has been overestimated.

Evans and Long (1921, a) have reported that thyroidectomy in rats affected neither the onset of puberty, nor the lengths of the oestrual cycles. They also reported (1921, b) that feeding of fresh thyroid gland substance had no disturbing effect upon the oestrual cycles.

In view of the interest and importance of this question and of the fact that many of the thyroidectomized rats in the series of Evans and Long showed regeneration of thyroid tissue, thus vitiating their results, it was thought desirable to repeat the work, making sure of an actual hypothyroidism of the animals.

MATERIAL AND METHODS

Eighty female albino rats of from 34 to 150 days were selected from the general colony. Eighteen of these, selected at random, were used as controls for this and other experiments in progress at the same time. Fifteen of these controls remained in good condition throughout the duration of the experiment,

and are reported in detail in Table 1. Three controls developed a respiratory infection and were discarded.

A sham operation, in which the thyroid glands were exposed and touched, but left intact, was performed upon five other control rats. The results from this procedure will be discussed below.

Thyroidectomy was performed on the remaining fifty-seven rats. Of this number some few died under ether anesthesia or from the effects of the operation. Some developed poor health during the course of the experiment and were discarded. Some others were found at autopsy or biopsy to have regenerated considerable thyroid tissue. These were discarded from the thyroidectomized series and are reported as a separate group in Table 3.

The twenty-nine cases forming the basis of this report remained in good health throughout the observation period and showed little or no regeneration of thyroid tissue. Seven animals of the twenty-nine were thyroidectomized before puberty, at the ages of 38, 40, 41, 39, 52, 56 and 34 days, respectively. The ages of the remainder at the time of operation varied from 90 to 150 days.

All animals were kept under the same environmental conditions in a well ventilated room, in which the temperature varied not more than four degrees (average eighteen degrees centigrade) during the whole period of five to six months. Four or five rats were confined to a cage 20x12x10 inches. A diet containing abundant mineral salt and vitamin constituents was fed, the food being kept before the rats at all times. This food, a modified McCollum mixture, contained the following constituents per hundred pounds:

Whole wheat flour	62.5 lbs.
Skim milk powder	15.0 "
Casein	15.0 "
$CaCO_3$	1.5 "
NaCl	1.0 "
Lard plus cod liver oil	5.0 "

In addition, fresh cabbage or lettuce and corn were fed weekly.

The health condition of this series was given especial attention. The bedding was changed often; the rats were kept

free from vermin; the teeth were kept at proper length, and undried food was fed on occasion. All rats reported upon maintained normal growth and body weight and remained to all appearances in good health. These details are mentioned because it is our experience that any condition of undernutrition, disease, crowding of animals in small cages, or extreme variation of temperature upsets the normal oestrual rhythm. The physical condition of a female rat is quite accurately reflected in the oestrual cycles. Any infection, inanition or other abnormal condition is quickly shown by a lengthened dioestrum or rest interval. In fact, such a halting of the normal rhythm often indicates the incidence of infection before there is any loss of weight or other evidence of it.

In the removal of the thyroids from the experimental rats a careful though not elaborate technic was followed. The animal was anesthetized with ether and tied out on a small board under a binocular microscope magnifying ten diameters. The thyroids were then exposed. Fine silk ligatures were placed around the vessels entering each thyroid lobe at the anterior and posterior ends (superior and inferior thyroid arteries). The mass of thyroid tissue was then carefully separated from the capsule by the use of a flexible needle, care being taken not to injure the recurrent laryngeal nerve which runs along the mesial border of each lobe. If this is seriously injured by cutting or undue traction the animal often develops gasping or gagging, takes no food and dies in a day or so. If the operation is done carefully bleeding is slight, healing rapid and mortality low.

The parathyroids were located in each case and at least one left in situ. In some cases the parathyroid was left with circulation intact, the thyroid being teased from around it; in others the parathyroid was removed with the thyroid, identified, teased out and replaced. In no animal of this series was any symptom of parathyroid deficiency noted. In many, evidence of thyroid deficiency became apparent in the loss of fine, soft hair, and the growth of coarse, thin hair, much as in senility.

At the end of the experiment all of the thyroidectomized rats were autopsied or biopsied. All tissues suspected to be

thyroid were removed, fixed and sectioned. Eleven out of forty animals were found to have regenerated thyroid tissue to such an extent that they were discarded from the series. Nine of these eleven which showed regeneration had been thyroidectomized before 50 days of age, indicating a greater possibility of regeneration in young than in adult rats. No hesitancy is felt in considering the twenty-nine animals in Table 2 to be definitely lacking in thyroid secretion.

The oestrual rhythm was followed by means of the smear method developed in Stockard and Papanicolaou (1917) and by Long and Evans (1922). By this method the cycle is divided into five periods, distinguished by the varying character and combination of cell types, in the vaginal fluid, as determined by microscopic examination. The five periods are: preparation for oestrus (stage I), oestrus (stage II), post oestrus (stage III), repair (stage IV) and rest or dioestrum (stage V). It has been found that if the rats are used to being handled the procedure of withdrawing samples of vaginal fluid for examination affects in no wise the oestrual rhythm. The various stages present such different microscopic pictures that no difficulty is experienced in distinguishing them.

OBSERVATIONS AND DISCUSSION

Daily determinations of the stage of oestrous in all animals were made by the method given above. In the case of the control series observations were made from October to the following June. The twenty-one experimental animals which had arrived at puberty some time before thyroidectomy was performed showed in this period before operation oestrual cycles of exactly the same average length as the control series, viz., 4.8 days.

In thirteen of the twenty-nine animals of the experimental series the oestrual rhythm was disturbed for one or two cycles immediately following thyroidectomy, these cycles being considerably lengthened (varying from eight to sixteen days).

It is highly probable that this effect is not to be ascribed to thyroid deficiency per se, but rather to the severe trauma and, in some cases, slight infection. This is further borne out by the fact that four of the five control animals which were traumatized showed a similar lengthening of the cycle immediately after

TABLE 1

Showing Lengths of Oestrous Cycles, in Order of Occurrence, in Control Series

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS
275	5,6,4,4,5,4,5,5,4,4,5,5,7,6,4,6,5,6,4,5,4,5,5,5,4,4,5,5,4,5,5,4,5,6,5,5,5,4,5,4,5,4,5,4,4,5,5,4,5,5,4,5,5,5.	52	249	4.8
276	6,5,5,5,6,5,5,5,4,4,5,6,5,4,4,5,6,5,4,5,5,5,5,4,5,5,5,4,5,5,5,6,5,4,5,5,5,4,5,5,5,5,5,5,5,5,5,5,5,5,5,5.	49	240	4.9
222	5,5,6,5,4,4,5,5,6,4,4,5,4,5,6,4,5,5,4,5,6,5,5,5,4,4,5,4,5,5,5,4,6,6,4,5,5,5,4,5,5,6,4,5,5,5,4,5,5,5,4,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5.	51	246	4.8
284	5,6,4,5,6,6,5,4,5,6,5,5,5,5,4,4,6,7,5,5,5,6,5,5,5,5,5,5,5,4,5,5,5,5,4,6,6,4,5,5,5,4,5,5,6,4,5,5,5,4,5,5,5,4.	49	245	5.0
287	5,4,6,4,5,6,5,4,5,5,4,4,5,5,4,5,5,6,5,4,4,5,5,5,5,5,5,4,5,5,5,6,6,7,5,5,5,4,5,5,4,5,4,5,5,5,5,4,6,5,5,4,4,5,6,4,5.	51	248	4.9
288	5,4,5,5,5,4,6,5,5,4,4,5,5,5,5,5,5,4,4,5,5,5,5,4,5,5,5,5,5,4,5,6,4,5,4,5,5,4,4,5,5,6,5,5,4,5,5,5,6,5,4,5.	52	250	4.8
297	5,6,5,6,4,4,6,4,6,5,5,4,5,5,5,5,5,5,6,4,4,5,5,5,4,5,4,5,4,5,5,5,4,5,5,5,5,4,5,5,5,4,5,5,5,5,5,5,4,4,5.	50	241	4.8
298	4,5,5,4,5,5,5,5,4,4,5,5,5,4,4,5,5,5,4,4,5,5,5,4,5,5,6,5,5,5,5,6,5,5,4,4,5,5,5,5,5,6,4,5,4,5,5,5,4,4,5.	51	245	4.8
413	4,4,5,6,5,4,5,5,6,4,5,4,4,4,4,5,5,5,5,5,5,5,4,5,5,4,5,5,5,5,5,5,5,5,4,4,5,5,5,5,5,6,4,5,4,5,5,5,4,5,6.	51	245	4.8
564	5,4,5,5,5,4,4,6,4,5,5,5,5,5,5,6,5,5,5,5,7,5,4,5,4,5,5,5,5,6,4,5,4,5,5,4,5,4,5,4,4,5,5,5,5,6,5,5,5,5.	51	244	4.8
565	5,6,6,5,7,5,4,5,6,4,5,4,5,5,5,5,5,4,5,5,4,5,5,4,5,5,6,5,5,5,5,5,5,4,5,4,5,4,5,5,5,5,5,5,5,5,4,4,5,5,5,4.	50	243	4.9
566	6,4,6,6,5,5,5,5,4,5,5,5,5,4,5,5,4,5,5,4,5,5,5,5,5,5,4,5,5,5,4,5,5,4,5,5,4,5,5,5,5,5,5,5,5,5,5,4,4,5,5,6.	49	243	4.9
586	4,4,5,4,4,5,5,5,5,4,5,5,5,4,4,5,5,5,6,6,5,4,4,6,5,4,4,4,5,5,5,4,5,5,5,5,5,4,5,5,5,4,5,5,5,5,4,4,5,5,5,5,5,6,5.	51	248	4.9
587	5,5,5,5,5,4,5,5,5,5,4,4,4,5,5,5,5,5,4,5,5,5,5,4,4,5,5,5,4,5,6,4,5,4,5,4,4,5,4,5,5,5,5,4,5,5,5,4,5,6,5,4,5,4.	52	246	4.7
588	5,5,5,5,5,4,4,5,5,5,5,4,5,5,5,4,4,5,5,5,5,5,5,6,4,5,5,5,6,4,4,5,5,5,5,5,5,4,5,5,6,4,5,4,5,6,4,5,5,6,4,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5.	51	242	4.7
	Totals	51	245	4.8
	Average	760	3,675	....
	Standard deviation	50.7	245	4.8
		..	....	±0.1

TABLE 2

Showing Lengths of Oestrous Cycles in Thyroidectomized Rats

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS	AGE AT FIRST OESTRUS DAYS	REMARKS
102	4,5,4,6,7,7,4,5,7,7,4,7,6,5,4,5,5,4,7,8,4,6,6	23	127	5.5	..	
109	(11),6,6,4,4,5,7,7,7,10,8,7,8,7,6,5,6,7,7,7	19	124	6.5	..	
125	7,5,6,7,4,8,5,4,6,7,5,6,7,8,6,6,9,5,6,5	20	122	6.1	..	
496	(13),5,6,3,5,6,6,5,4,4,5,6,5,9,5,5,5,5,5,6,8,5	21	113	5.4	76	
613	6,7,4,4,5,4,6,4,6,5,5,4,6,5,5,5,4,5,5,5,5,8,7,6,6	25	132	5.3	62	
884	*[11],[8],[7],4,7,8,8,8,12,7,6,6,4,7,7,7	13	91	7.0	53	First oestrus 15 days after thyroidectomy
886	*[10],[5],[6],7,6,8,5,5,7,4,5,6,6,6,6,6,7	14	84	6.0	61	First oestrus, 21 days after thyroidectomy
915	*[8],[8],[6],6,5,5,6,4,6,10,7,5,6,9,8,7	13	84	6.5	60	First oestrus, 19 days after thyroidectomy
555	(12),5,4,4,5,5,5,9,6,6,6,5,6,5,6,5,6,5,5,5,5,4,5	22	117	5.3	57	
165	(11),6,5,6,9,13,7,8,5,8,7,4,6,5,10,6,6,6,9,8,7	20	141	7.0	..	
245	(17),8,5,8,8,7,5,6,7,7,6,7,8,7,6,6,6,7,5,6,6	20	131	6.6	..	
257	5,11,5,5,5,5,5,6,5,5,7,8,4,8,7,10,6,6,7,5,5,5,5,7	24	147	6.1	..	
298	(8),4,5,10,7,4,5,6,6,5,6,6,5,7,4,12,8,7,9,7,4,6	21	133	6.3	..	
553	(16),(12),7,5,5,4,5,4,5,7,6,5,7,5,5,5,8,7,6	17	96	5.6	60	
301	6,6,10,8,10,8,10,7,6,7,7,7,7,5,5,5,6,6,6,6	20	138	6.9	..	
578	(10),5,5,5,5,5,8,5,4,7,6,8,6,5,6,5,5,6,5,5,6,10,6,6,7	24	141	5.9	69	
597	(9),8,4,6,6,6,4,6,5,6,4,4,7,5,5,6,4,5,6,6,7,6,5,6,6	24	133	5.5	77	
599	(9),6,8,5,8,9,9,7,8,6,6,7,9,6,7,5,5,6,6,5,5,5,7	22	145	6.6	71	
783	6,5,5,6,5,7,8,6,7,8,6,6,6,7,7,7,7,5,5,6,7,6,7	23	145	6.3	54	
828	5,6,5,5,6,4,4,7,5,6,6,5,5,5,4,5,3,5,6,4,6,7,6,5,7	25	132	5.3	58	
838	(12),7,7,4,5,4,5,7,5,10,5,5,5,4,9,4,5,4,5,5,5,4,6,5	23	125	5.4	64	
844	*[9],[5],[7],5,12,5,5,6,4,6,6,4,4,5,5,5,6,6,5	16	89	5.6	68	First oestrus, 29 days after thyroidectomy
846	(8),5,5,6,5,9,6,6,5,6,5,5,4,6,5,5,5,5,5,5,6,4,6,5,5	24	129	5.4	62	
799	6,4,5,4,4,4,5,8,7,4,5,7,4,4,7,5,6,4,5,5,5,4,5,5,5,6	26	133	5.1	66	
854	(11),7,9,6,4,5,5,3,6,5,5,5,6,5,6,4,4,5,5,5,6,5,9,6	23	126	5.5	53	
862	*[12],[6],[8],8,6,6,5,11,7,5,6,5,5,8,6,6,7	14	91	6.5	72	First oestrus, 20 days after thyroidectomy
864	*[10],[7],[15],9,5,8,10,5,5,4,4,5,6,5,5,4,5,5,6,5,7	18	103	5.7	58	First oestrus, 2 days after thyroidectomy
874	*[12],[7],[5],6,5,6,7,5,4,4,5,6,4,5,5,4,6,6,5,5,6,6,6,7	21	113	5.4	55	Thyroidectomized on day of first oestrus
878	[10],[7],[10],6,7,7,6,5,5,6,5,6,5,8,7,6,5,5,6,7,5,5	19	112	5.9	80	First oestrus, 3 days before thyroidectomy
	Totals	594	3,497	....	....	
	Average length of cycle	..	....	5.9	....	
	Standard deviation	..	....	±0.5	....	

Parentheses, ( ), around numbers indicate lengthened cycles immediately following thyroidectomy. These figures were not used in the calculations.

An asterisk, *, indicates that the animal was thyroidectomized some time before puberty.

Brackets, [ ], around numbers indicate cycles immediately following the first establishment of oestrus at puberty. In each such case the figures for the first three cycles were not used in the calculations.

the sham operation, followed by a re-establishment of the normal rhythm. Experience in adrenalectomy also indicates that in all such cases of operative trauma the cycles are temporarily arrested in the dioestrum.

These abnormally long cycles immediately following thyroidectomy are indicated in the table by parentheses () and were not used in calculations to obtain the average lengths. In eight cases there was no, or only a very slight, arrest of the rhythm after the operation. In all of the thyroidectomized animals reported upon the rhythm was re-established, but the cycles did not return to normal length. In each case the cycles became longer on the average, and less regular, as may be seen by examination of Table 2. This irregularity and lengthening was more noticeable in some rats than in others.

In eleven thyroidectomized rats which had regenerated much thyroid tissue, and which are treated separately, this irregularity was much less marked. In fact, several of them showed an average length of cycle nearly the same as that of the controls. It is significant that this regularity was only gradually recovered, presumably coincident with the regeneration of the thyroid. See Table 3.

In every case of a lengthened cycle the dioestrum or rest interval was the period involved, occupying from three to fifteen days as against two days in the average normal cycle. None of the other stages of the cycle showed any detectable abnormality. Thyroidectomized females in stage II showed the same heat reactions when placed with a male as did their normal controls.

In the thyroidectomized series a total of five hundred and ninety-four cycles, or an average of about twenty-one per animal was followed, giving a total average length of 5.9 days per cycle as against 4.8 days for normal rats. In obtaining this average both the lengthened cycles immediately following thyroidectomy and the first three cycles following puberty were omitted in the calculations. The first few cycles in a young rat are very often irregular (Long and Evans, 1922).

The seven animals which were thyroidectomized from three to twenty-nine days before the establishment of oestrus showed no postponement of puberty. The ages at which this occurred in these animals were well within the normal limits.

TABLE 3

Showing Lengths of Cycles in Thyroidectomized Rats in Which at Autopsy Regenerated Thyroid Tissue was Found

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS	AVERAGE LENGTH OF LAST 10 CYCLES DAYS
829	(10),7,6,6,5,7,8,6,5,5,7,6,6,5,5, 4,6,5,5,4,6,5,5,4,4	24	132	5.5	4.8
912	[7],[9],[6],7,7,6,7,5,8,6,6,5,6,6, 5,4,4,6,5,5,5,4,5,4	21	116	5.5	4.7
911	[11],[8],[8],9,6,6,7,5,7,6,4,6,5,5, 5,6,6,4,6,4,5,4,4,5	21	115	5.5	4.9
913	[7],[10],[7],6,8,8,8,6,7,6,5,5,7,6, 5,4,5,5,5,5,4,6,4,5	20	112	5.6	4.8
908	[8],[9],[7],6,5,7,7,6,8,5,6,6,5, 5,4,5,5,5,5,4,6,4,5	20	108	5.4	4.7
877	[9],[8],[6],7,8,6,6,5,6,5,5,7, 6,5,4,5,5,4,5,4,4,5	19	102	5.4	4.7
832	(14),7,6,7,5,4,5,7,7,6,6,6,5,5,4,6, 4,6,5,5,5,5,4,6,5,4	25	135	5.4	4.9
840	[8],[7],[7],6,5,8,7,7,6,7,5,4,6,5, 5,5,4,5,5,4,4,4,5,5	21	112	5.3	4.6
909	[13],[8],[5],7,5,5,6,7,5,8,5,5, 4,4,6,5,5,5,4,4,6,5	19	101	5.3	4.8
845	[10],[7],[6],5,6,6,3,5,5,4,5,6, 5,6,4,5,5,5,6,4,5,5	19	95	5.0	5.0
847	(11),7,6,6,5,6,6,7,6,5,4,5,5,6,4, 5,5,5,4,5,5,5,6,4,5	24	127	5.3	4.9
	Totals	233	1255	....	....
	Average length of cycles (days)	....	....	5.4	4.8
	Standard deviation	....	....	±0.1	±0.1

For explanation of symbols see table 2.

The unoperated control animals showed normal cycles throughout the time of observation. The average duration of these cycles (4.8 days) and the lengths of their component stages correspond closely to data from other rats in this laboratory, and to figures given by Long and Evans (1922).

After making due allowance for the effect of operative trauma a difference of one day in the average lengths of cycles of control and thyroidectomized animals seems too great and too consistent to be accounted for by chance. The first possible explanation that offers itself is, of course, that normally the thyroid exercises a stimulating action on those cells of the ovary that elaborate a hormone which is responsible for the cyclic changes of the reproductive tract. That the ovary does produce such a hormone is rather convincingly shown by both the effects of ovarian extirpation and of the administration of ovarian extracts (Allen and Doisy, 1923; Doisy, et al., 1924; Frank, et al., 1925). According to this view thyroidectomy removes the rather constant stimulus to the ovarian cells. As a result, the time between the production of successive physiologic doses of ovarian hormone is increased, and the dioestrum of the cycle is correspondingly lengthened. The evidence as yet is deemed insufficient to justify a definite statement that such is the case. In fact, the indications are that in this interaction the ovary is the stimulating gland. That is, the ovarian hormone, besides initiating the growth changes of the genital tract, causes increased activity in the thyroid gland. This is shown by the enlargement of the thyroid at puberty, menstruation and pregnancy (Marine, 1923; Daly and Strouse, 1925).

Another possible explanation is that the thyroid through its action on other body cells has an indirect effect upon the ovary. It has been found, as will be reported in a subsequent paper of this series, that activity affects markedly the length of the dioestrum. Female rats kept in activity cages, in which the voluntary activity is much greater than when in stationary cages, almost invariably show very short dioestrual intervals. Incomplete data from this laboratory indicate that in a considerable proportion of cases, thyroidectomized animals in recording cages show considerably less than normal spontaneous activity (Hoskins, 1925). It is suggested that ovarian activity

varies roughly with the general activity of the animal, and that the effect of thyroidectomy on the oestrual cycle is a secondary one, the primary effect being upon general metabolism, bodily activity and vigor.

SUMMARY

1. A study of oestrual cycles following thyroidectomy was made in forty rats, eleven of which regenerated considerable amounts of thyroid tissue.

2. In case of the twenty-nine animals in which complete or nearly complete ablation was secured the first and sometimes the second cycle following the operation were often much lengthened. This is interpreted, however, as due to trauma, or slight infection, as it also occurs in rats upon which a sham operation is performed.

3. The succeeding cycles, over a period of five months, showed an average lengthening of about one day above those in normal controls under the same environmental conditions.

4. The eleven animals which regenerated much thyroid tissue showed at first a lengthening of the cycles, and then a gradual return to the normal length.

5. Thyroidectomy at an age considerably before the establishment of the oestrual rhythm seemed to have no effect on the age of puberty.

6. Possible explanations for the lengthened dioestrum following thyroidectomy are suggested: (a) that normally the thyroid exercises a stimulating influence on the ovary, and that removal of this stimulus allows the cycle to be lengthened; (b) that ovarian activity varies with the general bodily activity and that thyroidectomy affects the oestrual cycle through its effect upon metabolic processes.

It is a pleasure to acknowledge indebtedness to Professor R. G. Hoskins for generous advice and criticism.

BIBLIOGRAPHY

Allen, E. & Doisy, E. A.: 1923. An ovarian hormone. J. Am. M. Ass. (Chicago), **81**, 819 (Sept. 8.)

Daly, P. A., & Strouse, S.: 1925. The thyroid during pregnancy. J. Am. M. Ass. (Chicago), **84**, 1798 (June 13).

Doisy, E. A., Ralls, J. A., Allen, E. & Johnston, C. G.: 1924. The extraction and some properties of an ovarian hormone. J. Biol. Chem. (Balt.), **61**, 711 (Oct.).

Evans, H. M. & Long, J. A.: 1921 (a). The effect of thyroidectomy on the

oestrus cycle of the rat. Proc. Am. Ass. Anat., Anat. Rec. (Balt.), **21**, 61.

Evans, H. M. & Long, J. A.: 1921 (b). The effect of thyroid feeding on the oestrus cycle of the rat. Proc. Am. Ass. Anat., Anat. Rec. (Balt.), **21**, 61.

Frank, R. T., & Gustavson, R. G.: 1925. The female sex hormone and the gestational gland. J. Am. M. Ass. (Chicago), **84**, 1715 (June 6).

Gley, E.: 1917. The internal secretions; their physiology and application to pathology. Hoeber, N. Y.

Hammett, F. S.: 1925. Inter-glandular associations. This Journal, **9**, 297 (July-Aug.).

Hoskins, R. G.: 1925. Endocrine factors influencing bodily vigor. Proc. Ass. Study Internal Secretions, J. Am. M. Ass. (Chicago), **85**, 298 (July 25).

Long, J. A., & Evans, H. M.: 1922. The oestrus cycle in the rat and its associated phenomena. Memoirs Univ. Calif. (Berkeley), **6**, Univ. of Calif. Press.

Marine, David: 1923. Importance of our knowledge of physiology in control of thyroid diseases. Arch. Int. Med. (Chicago), **32**, 811 (Dec.).

Stockard, C. R., & Papanicolaou, G. N.: 1917. Existence of a typical oestrus cycle in the guinea pig, with a study of its histological and physiological changes. Am. J. Anat. (Balt.), **22**, 225 (Sept.).

Vincent, S.: 1925. Internal secretions and the ductless glands. Physicians & Surgeons Book Co., N. Y., p. 336.

Book Reviews

DIABETES: ITS TREATMENT BY INSULIN AND DIET. A HANDBOOK FOR THE PATIENT. Orlando H. Petty & Wm. H. Stoner, 1925. F. A. Davis Co., Phila. Pp. 133.

This diabetic primer includes chapters on the nature of diabetes; foods, salts and vitamines; measuring foods; methods of estimating diet; testing urine for glucose; insulin and its home administration; diatetic hygiene; recipes of a number of standard dishes with their food values; and selections from the Atwater Bulletin on composition of foods. The presentation seems to be somewhat too technical for the class of readers who would presumably find it most useful, but the fact that it is now appearing in a second edition indicates that it has found a useful place.—R. G. H.

CONTRIBUCION AL ESTUDIO DE LAS RELACIONES ENTRE LA HIPOFISIS Y LOS CENTROS DIENCEFALICOS. M. L. Sánchez, 1924. Univ. Nac. de Mexico, Fac. de Med., Mexico, D. F. Pp. 262.

As a doctorate thesis from the Mexican National University the author presents a study of the hypophysis and the related diencephalic centers. The first section reports a comparative anatomical investigation made in bathrachians, guinea pigs, rabbits, cats, cattle and man. This is followed by a section on histology and one on experimental results from extirpating the hypophysis and from injury of the tuber cinereum. Five clinical studies are then given in some detail of cases in which the hypophysis and diencephalic centers were affected. It is concluded that a functional relationship exists between these structures.—R. G. H.

PATHOLOGIE DU SYMPATHIQUE. Laignel-Lavastine, 1924. Librairie Felix Alcan, Paris.

The author has gathered into a volume of 1000 pages practically all that is known of the sympathetic system. The normal and the pathological anatomy is treated, first, of the sympathetic elements and then of the sympathetic system. This is followed by an exhaustive discussion of the physiology

and pathological physiology of the system. The third or clinical part is devoted to the syndromes classified in relation to the different systems of the organism: skin, muscles, bones, joints, circulatory, and nervous system, etc.

Of special interest are the original studies of the author on the solar plexus, his observations on the "tache blanche" and the classification of several hitherto unclassified diseases as belonging to the sympathetic field. It will not be amiss to remark, however, that, since what is known of illness is to a great extent reduced to sympathetic disturbances, there is hardly a disease which should not be regarded as at least partially "sympathetic."

In spite of the undeniable merit of the book one must realize that the long and diligent study on the pathological anatomy refers to lesions, that are anything but specific, hence it is hardly fair to call it "Pathological Anatomy of the Sympathetic." Similar comment might be made regarding the physiology, since our knowledge of the sympathetic centers is very little more than a blank. What we know is almost only a phenomenology of interrelation of which the determining points escape our observation.

All in all this is a valuable book, especially as a reference, that errs only in offering a perhaps premature systematization that may be misleading and by unjustified generalizations create new errors in the medical field. Should it be possible—to cite an instance—to demonstrate that the sympathetic is the nervous system of the mesodermic formations and, consequently, its role the maintenance of co-operation among the several organic systems, then perhaps its working could be understood. An elucidation might then follow of what we are still forced to call "functional" diseases, regarding only the symptoms which strike our eye, instead of looking for the "primum movens."

—G. V.

Abstract Department

Fixing of cholesterol in the nervous system in vitamin B deficiency (Die Bindung des Cholesterons im Nervensystem bei Mangel an Vitamin B). Verzár (F.), Kokas (Ester) & Arvay (A.), Arch. f. d. ges. Physiol. (Berl.), 1924- **206**, 666-674.

In rats and pigeons on vitamin B deficient diets the cholesterol content of nerves decreases, and that of cholesterol esters increases to a greater extent. The changes are believed due to dysfunction of the adrenal cortex.—A. T. C.

Hypertrophy of the adrenal cortex with vitamin B deficiency (Die Hypertrophie der Nebennierenrinde bei Mangel an Vitamin B). Verzár (F.) & Péter (F.), Arch. f. d. ges. Physiol. (Berl.), 1924, **206**, 659-565.

The cortex, and not the medulla, is affected. The ratio of medulla to cortex is in normal rats 1:9; in normal rabbits, 1:8. The corresponding ratios after vitamin deficiency are 1:14 and 1:12.
—A. T. C.

The influence of atropin upon the vascular response to Adrenalin (Über die Bedeutung der Atropinisierung für den Blutgefasseffekt des Adrenaline). Wehland (N.), Skandin. Arch. f. Physiol. (Leipz.), 1924, **45**, 211-235.

Pithed frogs were used. Adrenalin following atropin gave vasodilation. A similar action of adrenalin followed after perfusion with a Ca-free solution. The author believes that atropin paralyzes the vasoconstrictor sympathetic nerve endings but does not influence the vasodilator sympathetic nerve endings.
—G. E. B.

The influence of diet on the action of certain internal secretions. V. (Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe. V.). Abderhalden (E.) & Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **207**, 222-227.

Adrenin has a stronger action (as measured by the ensuing hyperglycemia) on rabbits fed an acid diet. Since this action is inhibited by ergotamine, it must depend on increased irritability of the sympathetic system, and the tonus of the sympathetic can therefore be influenced by diet. Ergotamine does not affect any change of reaction to **insulin** on different diets; the action of in-

sulin is independent of the sympathetic nervous system. Rats on carbohydrate poor or free diet, and rabbits on an acid diet, following glucose injection show more marked hyperglycemia than control animals on carbohydrate rich diet.—A. T. C.

Observations concerning obesity with report of cases of endogenous type. McKinlay (C. A.), Minnesota Med. (St. Paul), 1925, **8**, 354-358.

One case of endogenous obesity due to alteration of **thyroid** function is reported that illustrates a phase of the cycle variation of thyroid function occasionally observed. Another case of endogenous obesity with lowered basal metabolism is reported. This patient lost weight after the use of a low calorie diet and thyroid extract. In the obese, lack of weight loss after lowered food intake and sufficient exercise suggests a rational basis, under proper control, which includes estimation of the heat production of the body, for the addition of the use of thyroid extract. In a series of 33 cases of obesity, 28 classified as simple and 5 as **pituitary** in origin, the basal metabolism was normal in 23 cases, above 10% in 9, and below in 9. Signs of endocrine disease were found in 4 of the 9 patients with subnormal basal metabolism.

—Author's Abst.

Relation between vitamins and hormones. Scheer (K.), Ztschr. f. Kinderh. (Berl.), 1925, **39**, 166-173.

The administration of **thyroid** to young white rats which have been upon a vitamin free diet causes a prompt reduction in weight, and death is hastened. The symptoms of avitaminosis are also intensified. **Testicular** extract has a similar, though weaker, action. **Thymus** extract favors increase in weight and growth, and lengthens life, obviating in part the symptoms of avitaminosis. There is thus a direct connection between the growth vitamins and the thymus hormone.—Physiol. Abst., **10**, 225.

Ovarian follicular hormone: distribution in human genital tissues. Allen (E.), Pratt (J. P.) & Doisy (E. A.), J. Am. M. Ass. (Chicago), 1925, **85**, 399-405.

A determination of the amount of active substance extracted from different human genital tissues is made by Allen, Pratt and Doisy. This is measured in rat units by means of a decisive anatomic and physiologic reaction of the genital tract of the spayed rat to injected lipoid extracts. The follicular hormone is present in greater concentration in large ovarian follicles of women than in those of pigs. In pigs and cows, the secretion of this hormone ceases or wanes rapidly following ovulation; in women, it is continued after ovulation by the **corpus luteum** for a considerable period. It seems possible that this may prove to be one of the prin-

cipal determining factors in the difference between the estrous cycle of lower mammals and the menstrual cycle of primates. Extracts have been made of placentas from women and cows which give the same growth reaction in test animals as does the ovarian follicular hormone. The human corpus of the first and third months of pregnancy contains some active substance, but the placenta contains much larger quantities. The evidence presented indicates that the corpus can be excised as early as 20 days following the last menstruation without interfering with normal gestation; consequently, this endocrine function of the corpus in woman during this time does not seem a necessary one. Two possibilities present themselves to explain placental endocrine function: either (1) the hormone extracted from the placenta is elaborated there, or (2) it is retained there after being formed in the ovarian follicles or (in woman) in the corpus luteum. Further experimental evidence is necessary to settle this point.—A. M. A.

Demonstration of the female sex hormone in the circulating blood. Frank (R. T.), Frank (Marie Louise), Gustavson (R. G) & Weyerts (W. W.), J. Am. M. Ass. (Chicago), 1925, **85**, 510.

The blood of five sows in estrus, five not in estrus, and the blood of one bull was collected. An alcohol benzene extract of each specimen was injected into one or more castrated rats, and the vaginal smear watched. None of the anestrous bloods, or the male blood, gave a positive reaction. Of the five bloods obtained from estrous animals, four gave positive results with a total dosage of 75 mg. of crude extract. With present methods of extraction at least 300 cc. of estrous blood is necessary to obtain 75 mg. of extract necessary for the test. Even with the present crude and not quantitative methods of concentration these results show that: (1) the female sex hormone can be recovered from the circulating blood, and (2) the quantity in circulation is greater during estrus than during the interval. It will be sought to devise quantitative methods of extraction which will permit the study of the amount of sex hormone present under physiologic conditions, such as prepuberty, puberty and the fertile and infertile sex cycle, as well as in pathologic states such as amenorrhea, sterility and menorrhagia.
—R. G. H.

Experimental hermaphroditism and the antagonism of the sex glands. I. Intrarenal ovarian transplantation. Indicators of feminine and masculine hormone effects in guinea pigs (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. I. Die intrarenale Ovarientransplantation. Die Indikatoren des weiblichen und männlichen hormonalen Effekts bein Meerschweinchen). Lipschütz (A.), Arch. f. d. ges. Physiol. (Berl.), 1925, **207**, 548-562.

A simple method of intrarenal ovarian transplantation is described which can be carried out extraperitoneally. It produces with male guinea pigs, castrated, or with fragments of testes, almost always positive results, in some months, as judged by the feminine hormone effects of the condition of nipples and mammae.
—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. II. Hormone action and condition of testes-fragments in experimental hermaphroditism (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. II. Die hormonale Wirkung und das Verhalten von Hodenfragmenten bei experimentellem Hermaphroditismus). Lipschütz (A.) & v. Voss (H. E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **207**, 563-582.

In most cases where the testis-mass is reduced to a fragment ovarian intrarenal implantation produces maximum hormonal breast effects within 10 months, in the majority of cases milk being produced. The results, contrasted with those when ovaries are implanted without castration, indicate that the testes antagonize the feminine hormone. In many animals the masculine characteristics remained, and the testicular fragments frequently contained spermatozoa, indicating that the ovary does not definitely inhibit spermatogenesis.—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. III. The connection between the implanted ovarian mass and the latency time. Further observations on the conditions of the testicular fragments in experimental hermaphroditism (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. III. Ueber die Beziehungen zwischen der implantierten Ovarialmenge und der Latenzzeit. Weitere Beobachtungen über das Verhalten von Hodenfragmenten bei experimentellem Hermaphroditismus). Lipschütz (A.) & v. Voss (H. E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **207**, 583-595.

The latent period before the effects of the feminine hormone are observed after ovary implantation into partially castrated male guinea pigs varies with the mass of ovarian tissue implanted. The ovary of a 16-day-old female produces effects in a male after 2 or 3 weeks (hypertrophy of breasts), although in the original female these would not have been produced for 6 or 8 weeks. This may be due to an accelerated follicular development in the implant.
—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. IV. The antagonistic influence of the testis on the ovary. Sectional experiment (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. IV. Die an-

tagonistische Beeinflussung des Ovariums durch den Testikel. Der Entriegelungsversuch). Lipschütz (A.), v. Voss (H. E.) & Vesnjakov (S.), Arch. f. d. ges. Physiol. (Berl.), 1925, **208**, 272-292.

In a male uncastrated guinea pig, in which intrarenal ovarian transplantation has not produced during some months any feminine hormone effect, removal of testes results in the production of this effect after a short interval. Presence of the testes inhibits the effect, probably delaying follicular ripening, and increasing the tendency to degeneration of the implant.—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. V. The mechanics of action of the sectional experiment. Fractionation of the latency time (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. V. Ueber den Wirkungsmechanismus der Entriegelung. The Fractionierung der Latenzzeit). Lipschütz (A.), Lange (F.), Svikul (D.), Tiitso (M.) & Vesnjakov (S.), Arch. f. d. ges. Physiol. (Berl.), 1925, **208**, 293-317.

The latency time can be divided into vascularization (of the transplant) time, ripening time, and reaction time. Transplantation of a rabbit ovary into a castrated guinea pig never produces the feminine hormone action.—A. T. C.

Ovarian grafts. Experimental and clinical results as regards menstruation, fecundation and pregnancy (Greffes d'ovaires Résultats expérimentaux et cliniques concernant la menstruation, la fécondation et la grossesse). Tuffier (T.) & Bour (D.), Presse méd. (Par.), 1925, **33**, 1073-1076.

From a somewhat extensive review of the experimental and clinical literature and personal experience in 50 clinical cases Tuffier and Bour conclude that free ovarian grafts implanted during the genital life of the woman, and especially autografts, give very good results as regards the general health. Menstruation is reestablished usually in 3 to 5 months after the operation and persists at least 5 to 6 years. Experiences in animals and in women have proved that after this operation pregnancy can occur. Transplantation in the uterus of an ovary supplied with its vascular and nervous peduncle is a beneficial operation in well determined cases. The vascular peduncle being unharmed, the ovary is perfectly nourished, and the follicles arrive at maturity and can discharge ova into the uterine cavity. Fertilization is possible and pregnancy can often go to term, and healthy offspring be born. In every case, transplantation is beneficial since the ovary lives and functions afterwards, menstruation is not often disturbed in periodicity nor in duration, and since the woman, in a condition of general

good health, escapes the symptoms of early menopause. The only inconvenience arising from the transplantations, as in all partial operations on the utero-ovarian organs of women, is that in 50% of the cases there are slight pains before menstruation.

—R. G. H.

Activity studies on male castrated rats with ovarian transplants, and correlation of the activity with the histology of the grafts. Wang (G. H.), Richter (C. P.) & Guttmacher (A. F.), Am. J. Physiol. (Balt.), 1925, **73**, 581-599.

The basis for these experiments was the observation that the running activity of males castrated at an early age always remains on a low level, and that there are sex differences in activity which can be measured; the four-day cycle present in the female and absent in the male, and the higher running level of the female. Transplantation of ovaries into castrated males may produce a marked increase in activity. The amount of the increase in 17 out of 24 animals varied from 1.03 to 116 times the pretransplantation level. The remaining 7 animals showed a decrease in activity after the operation. Five of the castrated males after ovaries had been transplanted into them ran as much as normal females and considerably more than the average male. Four others reached the average for males, while the rest ran less than either males or females. In 4 of the animals the activity cycles characteristic of the mature female rat were produced, but were not quite so regular as they are in normal females. Very much less regular activity cycles were present in 9 other animals. The remaining animals showed no cycles at all. Twelve of the animals showed a change in body weight following transplantation, that is, the more rapid rate of growth of the castrated males was dimin'shed until the body weight curve closely approximated the body weight curve of the normal female. When the grafts were removed the body weight increased again to the male level. Five animals showed small and somewhat doubtful changes in body weight, while 7 showed no changes at all in body weight. Histological examination of the grafts showed that ovarian tissue was present in all animals with either a change in activity or body weight. The grafts contained graafian follicles, ova, and corpora lutea, but they did not present the histological picture of completely normal ovaries. The grades of activity and body weight changes were not correlated with definite histological differences in the grafts, except that in animals which showed neither an increase in activity nor a body weight change the grafts were completely absorbed. Because of the absence of any correlation between the activity changes and the histology of the grafts an attempt was made to determine whether the weight and activity changes might not be correlated with the histological picture on the basis of different degrees of vascularization

of the grafts. However, no such correlation could be established. —Authors' Summary.

The ovarian hormone. Zondek (B.) & Aschheim (S.), Klin. Wchnschr. (Berl.), 1925, **4**, 1388-1390.

The cytology of the vaginal secretion in the white mouse is closely dependent on the physiologic cycle of the ovary, as is also the hormone action of implanted material in the castrated animal. Zondek and Aschheim examined on this basis the action of different organs on the sexual cycle. Glandular and endocrine organs did not influence the sexual periods. Ovarian substance provoked the cycle in a few days. Only the wall of mature or nearly mature follicles or their liquid content is active. The only other organ which contains the active prnciple is the placenta.

—J. Am. M. Ass., **85**, 710.

The content of posterior pituitary secretion present in cerebrospinal fluid (Ueber den Gehalt der Cerebrospinalflüssigeit an Hypophysenhinterlappensekret). Miura (Yoshio), Arch. f. d. ges. Physiol. (Berl.), 1925, **207**, 76-84.

Experiments with cats show that the cerebrospinal fluid from the fourth ventricle contains a slight amount of the uterus-stimulating substance of the posterior pituitary. After removal of the pituitary the fluid ceases to possess this property.—A. T. C.

Medical treatment of pituitary neoplasm. Pardee (I. H.), J. Am. M. Ass. (Chicago), 1925, **85**, 513-515.

A brief review of the literature and four illustrative case reports are offered. The gradually increasing number of case reports in the literature and the experience of those working in the author's clinic are taken to indicate that all pituitary neoplasms, whether large or merely hyperplasias, should be given the benefit of medical treatment, provided vision is not in immediate danger of becoming lost. First, glandular extracts should be used, especially pituitary and pituitary extract, and, as a later resort, roentgen-ray treatment. Many patients under this procedure will be saved from a major operation, the outcome of which is often problematic. The types of cases most likely to respond to the foregoing method are those of pituitary hyperplasia and adenoma, which are not of the destructive type and do not seem to be growing rapidly. These often show symptoms of glandular disturbances elsewhere and will often develop erosion and enlargement of the sella, chiasmal pressure and, perhaps, signs of pyramidal tract pressure. The glandular therapy recommended is desiccated pituitary body by mouth and pituitary extract hypodermically. Combined with this, any necessary supportive or substitutive therapy should be given to other endocrine organs. Many patients recovered under the foregoing treatment.—R. G. H.

The effect of pituitary extract on the secretion and composition of the urine. Stehle (R. L.) & Bourne (W.), J. Physiol. (Lond.), 1925, **60**, 229-236.

Studied effect of pituitrin in normal fasting dogs with bladder fistulas. When the initial urine flow was high an antidiuretic effect was produced smilar to that in **diabetes insipidus.** With low initial flow diuresis resulted. The most striking results were obtained in chloride excretion which was increased as much as 74 times (minute rate). This effect was mostly suppressed when the dogs were anesthetized. The authors regard their results as most likely due to local effects in the kidneys rather than on body metabolism. Phosphate and urea excretion were also augmented but to a lesser degree than chloride.—R. G. H.

A case of dyspituitarism following encephalitis lethargica. Worster-Drought (C.), Brain (Lond.), 1925, **48**, 127-128.

A boy aged 14 developed encephalitis. Since convalescence he has gradually developed the picture now presented of general adiposity, normal genitalia, relative lymphocytosis, increased sugar tolerance, and a blood sugar curve suggesting dyspituitarism of the Dercum type. It is possible that the condition is due to involvment by encephalitic process of the nuclei of the tuber cinereum, rather than of the pituitary.—A. T. C.

The control of blood pressure with liver extracts. James (A. A.) & Laughton (N. B.), Canad. M. Ass. J. (Montreal), 1925, **15**, 701.

Protein-free extracts of liver effectually reduce the hypertension effects of **adrenin, pituitrin,** isoamylamine, and parahyroxyphenylethylamine in rabbits, and reduce their normal blood pressure to about 50 mm. of mercury for prolonged periods. With large doses death ensues. It is believed that the active substance is not choline or histamine.—A. T. C.

Extractives of liver possessing blood pressure reducing properties. Macdonald (W. J.), Canad. M. Ass. J. (Montreal), 1925 **15**, 697-701.

Extracts of liver, stated not to be of protein nature, but of which the method of preparation is not given, when injected into normal rabbits produced marked falls of blood pressure. In a number of cases of marked hypertension the majority showed definite fall in blood pressure, lasting after a single injection for from one to three days.—A. T. C.

Action of insulin (Beitrag zur Kenntnis der Wirkungen des Insulins). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **208**, 135-145.

Experiments on intestine and uterus of mammals show that commercial insulin preparations produce a paralyzing action on tone and automaticity of the intestine, due to their phenol content. Phenol-free preparations produce a characteristic increase of tonicity. Choline and adrenin action is strengthened. Acetylization of insulin preparations show that they contain slight amounts of choline. The authors believe that the apparent antagonism between insulin and adrenin is traceable to this choline content.

—A. T. C.

Trophic action of insulin. Ambard (L.) & Schmid (F.), Bull. Soc. méd. d. hôp. (Par.), 1925, **49**, 904.

Ambard and Schmid describe a case in a woman, aged 67, with an apparently tuberculous skin lesion on one foot, which developed into a deep and large ulcer (20 by 20 cm.) of the infectious type. As various measures used during 5 months did not prove successful, wet dressings with insulin were tried (12 units twice a day). No changes were noted the first 12 days; then granulations appeared, followed by complete healing in about 10 days. In other cases small ulcers healed in a week, after other measures had failed. In only one case out of 14 did insulin fail to give results. In the beginning the insulin was given subcutaneously, afterward the wound was powdered with it. The action is ascribed to an exaggerated cellular activity of the tissues resulting from stimulation of the carbohydrate metabolism.

—J. Am. M. Ass., **85**, 473.

Insulin in treatment of ulcers. Chabanier (H.), Lumière & Lebert, Bull. Acad. de méd. (Par.), 1925, **94**, 782-784.

Chabanier, Lumière and Lebert treated with insulin 10 non-diabetic patients with varicose ulcers. Two daily injections of 40 units each were given and dressings with insulin ointment were applied locally. Neither special diet nor rest were prescribed. In one of the patients, aged 61, with two ulcers of 20 years' standing, under the general and local insulin treatment, one ulcer healed in 19 days, the other in 30 days. Another patient, aged 51, with recurrent ulcer of the leg the last 10 years, was cured in 10 days, the ulcer being completely healed. In a diabetic girl treated during the last 2 years with large doses of insulin (80 units daily) an ulcer had developed on each sole in the last 3 months. Applications of insulin ointment were followed by total healing of the ulcers in less than a month.—J. Am. M. Ass., **85**, 706.

Changes in the physiological action of insulin induced by exposure to ultraviolet light. Ellis (M. M.) & Newton (E. B.), Am. J. Physiol. (Balt.), 1925, **73**, 530-538.

Insulin solutions exposed in an atmosphere of nitrogen in

transparent fused-quartz tubes to the action of the ultraviolet light from a mercury vapor lamp for periods of from 19 to 48 hours lost their power to produce hypoglycemia when injected into test animals. Some substance or substances were developed in these exposed insulin solutions which produced hyperglycemia when injected. Insulin solutions under nitrogen in pyrex glass test tubes which filter out most of the short rays did not lose their power to produce hypoglycemia when injected into test animals, after 48 hours' exposure under the mercury vapor lamp, although quantitatively the 48-hour samples seemed slightly less potent than the unexposed controls. These changes in the insulin solutions were not due to the presence of tricresol. Ozone and free oxygen in ordinary daylight destroyed the power of unexposed insulin solutions to produce hypoglycemia, but did not develop hyperglycemia-producing substances in one-hour treatments. A possible "activating" action of ultraviolet light on insulin in nondestructive exposures is mentioned.

—Authors' Summary.

Insulin treatment of leg ulcers. Faure-Beaulieu & David, Bull. Soc. méd. d. hôp. (Par.), 1925, **49**, 892-895.

Ten of Faure-Beaulieu and David's patients with leg ulcers presented hyperglycemia, while no sugar was detected in the urine. They were treated with insulin in dosage of 10 units subcutaneously twice a day. In one case the total amount of insulin was 1,600 units; usually, about 500 units. One woman with an ulcer 11 by 7 cm. in size and glycemia of 0.212 gm. per 100 cc. was cured in 2 months. She was given 480 units of insulin. A similar ulcer the year before took 7 months to heal. Another woman with an ulcer 7 by 9 cm. and glycemia of 0.241 gm. was completely cured in one month (320 units). One syphilitic woman had had a large and very painful ulcer for 4 years, rebellious to specific treatment. After 2 months' injections of insulin the ulcer, 14 by 10 cm., was reduced by a half. The glycemia in this woman was 0.216 gm.

—J. Am. Ass., **85**, 473.

Observations upon the action of insulin on the blood, with special reference to the cause of the condition known as hypoglycemia. Foshay (L.), Am. J. Physiol. (Balt.), 1925, **73**, 470-479.

It has been shown that insulin causes a reduction in the quantity of glucose in the dog's erythrocytes disproportionate to the reduction in the whole blood, and that it causes the same response in human blood. Moreover, it has been shown that insulin reactions can occur without hypoglycemia, both in man and in the dog, and that such reactions in the dog begin simultaneously with the reduction of the corpuscular glucose. This offers a probable explanation of the failures to find the blood sugar low in the majority of the cases of insulin reactions, for only the whole blood sugar was

measured. The train of symptoms and signs that follows administration of large doses of insulin, and at least the early subjective and objective phenomena of insulin overdosage, are not associated with a hypoglycemia per se, but rather with a cytoglycopenia—a status of glucose impoverishment within the cell. This is of importance in the treatment of diabetes, especially when large doses of insulin are used. For, as has been shown, the whole blood sugar determination, which is commonly used as the therapeutic guide, is not a reliable index of an approaching insulin overdosage. This is particularly true of a patient in coma, when the symptoms are absent and the signs are obscured, for then another large dose of insulin, given because the last whole blood sugar was still quite high, may lead to a fatal issue. Corpuscular sugar determinations are a reliable index of the physiological activity of insulin. They give evidence of degrees of action which are not obtained from whole blood sugar measurements.—Author's Summary.

Therapeutic uses of insulin in oily emulsion (Essais thérapeutiques avec l'insuline en émulsion huileuse). Hedvall (E.), Acta med. Scand. (Stockholm), 1925, **62**, 334-350.

Hedvall sought to develop a practical method of rendering less irksome the administration of insulin. A careful clinical study showed that an oily emulsion, injected intramuscularly or subcutaneously, is resorbed more slowly than insulin otherwise administered and its action persists longer. The resorption is not slow enough in case of intramuscular injection to permit only one injection daily. In many patients, however, a single injection of the insulin emulsion subcutaneously can take the place of two or more injections administered in the usual way. But with larger doses hypoglycemia may follow if there is only one injection a day, and the danger is too great to render the method of any practical advantage.—R. G. H.

The growth, development and prognosis of diabetic children. Joslin (E. P.), Root (H. F.), & White (Priscilla), J. Am. M. Ass. (Chicago), 1925, **85**, 420-422.

Joslin, Root and White have investigated this problem by studying the histories of 302 bona fide diabetic children. Of these, 162 died and 132 are alive. If a diabetic child gained weight before the discovery of insulin, it was considered an extraordinary event. When it did occur it was temoprary, and the weight quickly fell to below that at onset. The weight of the diabetic child treated with insulin increases. The increase in weight of 34 diabetic children treated with insulin over an average period of 18 months exceeds that of the normal child for the same length of time. An increase in height is present in the insulin-treated diabetic child, but it is distinctly less than that of the normal child. Unaided by insulin, no

girl in the series developed menstruation after the onset of diabetes. Since the use of insulin, 4 girls have begun to menstruate for the first time, and in another the onset of menstruation and diabetes were simultaneous. Menstruation ceased in 6 patients without insulin treatment, or became irregular soon after the onset of diabetes. The appearance of the boys has so changed that there is little doubt of their having matured. Of the 164 children treated without insulin, there remain but 12 alive. The 152 patients who died survived 2.4 years, and that constitutes the prognosis of the noninsulin-treated diabetic child. Of 130 children treated with insulin 120 are living.—A. M. A.

The liver in insulin hypoglycemia (Il fegato nella ipoglicemia da insulina). Villa (L.), Boll. soc. med.-chir. di Pavia, 1925, **37**, 105-115.

Insulin hypoglycemia is due to an action taking place chiefly in the liver, but in a smaller degree also in muscles; this action consists of the inhibition of glycolysis. **Adrenalin** stops the inhibitory action of insulin and restarts the glycolytic function of the liver; it is, therefore, a more rational antidote than glucose itself. —Physiol. Abst., **10**, 229.

Treatment of sprue by parathyroid extract. Field (C. P.), J. Roy. Army Med. Corps (Lond.), 1925, **44**, 456-457.

Successful treatment is recorded in a (pregnant) subject, with 0.1 gr. parathyroid extract twice a day, calcium lactate, 30 gr. daily, and a daily bowel wash of saline.—A. T. C.

The influence of Liebig's extract in experimental tetany (Ueber den Einfluss von Liebig's Extrakt auf die experimentelle Tetanie). Sinelnikoff (E. I.), Arch. f. d. ges. Physiol. (Berl.), 1925, **207**, 351-360.

Flesh feeding has no harmful influence on **thyroidectomized** dogs with undamaged parathyroids, while raw meat leads to and increases all the tetany symptoms in parathyroidectomized dogs. The actual poison of raw meat passes into the watery extract, and long cooked meat has no noticeable poisonous action. Liebig's extract in a dose of 4 to 5 gms. per kilo body-weight produces in parathyroidectomized dogs all the symptoms of tetany within 0.5 to 2 hours after introduction into the stomach. Raw flesh, broth, and Liebig's extract contain guanidine and methylguanidine. Guanidine in doses corresponding to the amount present in flesh extracts does not completely produce tetany, and is less active than Liebig's extract and raw flesh. The poisonous action of Liebig's extract is probably due to the combined action of methyl-guanidine, carnitine, oblitine, etc. The liver, as well as the parathyroids, exercises a definite protective function against guanidine.—A. T. C.

The after effects of thyroid extirpation (Beitrag zur Kenntnis der Folgen der Schilddrüsenexstirpation). Abderhalden (E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **208**, 476-486.

Experiments in guinea pigs show that there are marked differences in different individuals following thyroid extirpation.—A. T. C.

Tryptophan and thyroid function. Abel (A. R.), Backus (R. W.), Bourquin (H.) & Gerard (R. W.), Am. J. Physiol. (Balt.), 1925, **73**, 287-295.

White rats were fed on diets similar except for their content of tryptophan, thyroxin, and protein. The variations in the diets were: (1) protein as casein largely or entirely; (2) as zein and gelatin with the addition of tryptophan; (3) as zein and gelatin with no added tryptophan or thyroxin; (4) as zein and gelatin with the addition of thyroxin. Rats on the tryptophan-free diet developed characteristic symptoms leading to death. The thyroid gland showed a slightly increased cellularity. Minute amounts of tryptophan in the diet did not alter the symptoms but prevented any change in the thyroid. The symptoms once developed were not relieved by later adding tryptophan or thyroxin to the diet though tryroxin transformed some of the glands to the colloid state with evidences of atrophy. Thyroxin added to the tryptophan-free diet from the start rendered the thyroid colloid and very atrophic and prevented entirely the tryptophan-free symptoms, except emaciation and death. These facts indicate that: tryptophan is essential to the normal functioning of the thyroid; a large amount of the needed tryptophan is available for the thyroid from the tissues of the body; the thyroid is able to take up tryptophan from the blood in quantities approximating its needs, even when the total amount is so small that other tissues suffer from its lack; sufficient thyroxin from an outside source induces atrophy of the thyroid. Lack of tryptophan results also in extrathyroid disturbances leading to emaciation and death.—Authors' Summary.

Two cases of adolescent myxoedema accompanied by nephrosis, and in one case, tetany. Davidson (J. R.), Canad. M. Ass. J. (Montreal), 1925, **15**, 598-600.

A case of adolescent myxoedema, accompanied by nephrosis and by tetany of parathyroid origin, treated with thyroid and Collip's parathyroid extract. Davidson (J. R.), Canad. M. Ass. J. (Montreal), 1925, **15**, 803-808.

Thyroid treatment in the first case brought the basal metabolic rate to normal, and apparently decreased the nephrosis.

Thyroid and calcium treatment of the second subject caused the symptoms of myxoedema almost to disappear, while the tetany

convulsions markedly diminished in number and severity. Combined thyroid (by mouth) and Collip's parathyroid extract (subcutaneous injection) over a period of 6 months kept the basal metabolic rate within normal limits, and the serum calcium between 10 and 11.5 mg. per 100 cc. There was gradual improvement and almost complete elimination of convulsions in spite of many intercurrent infections to which the patient was extremely susceptible, and one of which ultimately proved fatal. The diagnosis was confirmed at postmortem.—A. T. C.

Iodin hyperthyroidism. Jackson (A. S.), Am. J. M. Sc. (Phila.), 1925, **170**, 271-283.

The number of cases of iodin hyperthyroidism has greatly increased, due to the popular demand for iodin in the treatment of goiter. In the series of 38 cases reported in this article 20 were observed within the past six months. Two cases terminated fatally. This condition had generally been termed **iodin-Basedow** in the literature, and consequently has been confused with exophthalmic goiter. Iodin should not be distributed promiscuously either in water or salt, but should be administered in exact amounts and under a physician's order. Even minute amounts of iodin are sufficient to initiate symptoms of hyperthyroidism in certain persons with adenomatous goiters. Iodin should be administered with particular care to children with adenomatous goiters; it should never be given to adults with this condition. Every child in the goiter belt between the ages of 10 and 20 years should receive small weekly doses of iodin for the prevention or treatment of colloid goiter. Iodin hyperthyroidism is rare in persons under 30 years of age. It develops only in the presence of an adenomatous goiter. The clinical syndrome may be clearly distinguished from that seen in toxic adenoma or exophthalmic goiter. Thrills, bruits and exophthalmos do not occur. If an early diagnosis is made medical treatment may abort the toxic symptoms. Thyroidectomy is indicated when the condition does not yield to medical measures. The pathological picture is not characteristic. Grossly, the gland has the typical appearance of an adenomatous goiter containing degenerated, cystic, fibrous and calcareous encapsulated nodules. Colloid may be seen in large amounts. The microscopical picture shows acini of variable size, lined with flat, cuboid cells, and filled with colloid. Fetal acini and occasional small areas of hypertrophic cells are found.—Author's Summary.

The physiological properties of substances from the isolated thyroid (Ueber die physiologischen Eigenschaften der Substanzen der isolierten Schilddrüse). Maloff (G. A.), Arch. f. d. ges. Physiol. (Berl.), 1925, **208**, 335-342.

Locke's solution, perfused through the isolated thyroid, con-

tains substances which increase the irritability of the sympathetic nerve endings, and thereby increase the sensitivity of the (isolated) liver vessels to **adrenin**, but have no effect on the isolated heart, the vessels of the isolated extremities, or the frog liver.—A. T. C.

The thyroid and the nervous system. Oswald (A.), Klin Wchnschr. (Berl.), 1925, **4**, 1053-1055.

Oswald attributes to the instability of the nervous system the degree of sensitiveness to administration of thyroid extracts. Tachycardia, nervousness, tremor or sweating has been produced by thyroid extracts experimentally only in fox terriers degenerated from inbreeding. He found that thyroid extract increases the action of pilocarpin, histamin and morphin. The bradycardia following an injection of pilocarpin is more pronounced and lasts longer under the influence of thyroid extracts. They sensitize the nervous system and the latter increases the action of the thyroid gland, which thus serves as an amplifier of the impulses. Thyroxin is not the full hormone because it does not act on the nerves regulating the blood circulation and on Auerbach's plexus. It is an artificial split product. Only the thyroglobulin is, in the author's opinion, the true hormone of the thyroid.—J. Am. M. Ass., **85**, 396.

Relation between experimental tuberculosis and the thyroparathyroid system (Rapporti fra tubercolosi sperimentale e sistema tiroparatiroideo). Salvioli (G.), Boll. Ist. Sieroter. (Milano), 1924, **3**, 197-240.

The dog is a useful experimental animal in the study of tuberculosis. After parathyroidectomy dogs are more resistant and after thyroidectomy more sensitive to the disease. If over-regeneration of the thyroid occurs, however, the infection is impeded. The author believes that thyroid treatment may be helpful.—P. M. N.

Studies on mitochondria. I. The changes occurring during experimental thyroid hyperplasia and its involution with iodine. Secoff (D. P.), Am. J. Pathol. (Bost.), 1925, **1**, 295-303.

Secoff has studied the mitochondrial variations during the developmental stages of hyperplasia induced in the thyroids of cats, rats, rabbits, guinea pigs, pigeons and chickens by high fat diets, and during compensatory hypertrophy in the guinea pig, as well as those occurring during the involuntary response produced by iodine. This report is concerned with his observations on the rat and guinea pig, although they were the same in all the animals studied. The number, morphology and distribution of the mitochondria in the thyroid cell vary directly with the degree of active hyperplasia or involution. During the developmental stages of active hyperplasia

the mitochondria increase in number, become filamentous and concentrate at the lumen pole of the cell. During involution the mitochondria decrease in number, become shorter and more scattered. Variations in the mitochondria, like the cycle of histologic changes, in the thyroid, depend upon the percentage-iodine, and therefore cannot be correlated with existing clinical classification of thyroid diseases. The relationship between variations in the mitochondrial constituents and the functional activities of cells is unknown. The specific affinity of the thyroid cell for iodine may offer a suitable method for inducing controllable mitochondrial alterations by which future studies may lead to a better understanding of the significance of such variations, and possibly the relationship between mitochondria and cellular activities.—J. P. S.

Myocarditis from thyroidin and iodine salts (Ueber die akute interstitielle Myocarditis durch Thyreoidin und Jodsalze). Takane (I.), Tr. Jap. Path. Soc. (Tokyo), 1923, **13**, 48.

The author gave to rats, guinea pigs and rabbits 0.005 to 0.08 gm. thyreoidin per 50 gm. body weight. After 7 days he found polymorphonuclear infiltration of the myocardium with degeneration of the muscle fibers. This inflammatory process reached its maximum grade in 12 to 13 days, and the animals usually died at about this stage. The process was most marked in the left ventricle. Experiments with inorganic iodides gave the same results.—J. P. S.

The basal metabolism of children with ichthyosis. Talbot (F. B.) & Hendry (M.), Am. J. Dis. Child. (Chicago), 1925, **29**, 770-772.

Basal metabolism studies lead to the conclusion that ichthyosis in the majority of cases is not due or related to hypothyroidism. Whatever seeming temporary improvement may result from the administration of thyroid extract must be explained by some other means than the direct action of thyroxin on the metabolism.

—M. B. G.

On the absorption by the hyperplastic thyroid gland of various forms of iodine introduced intravenously. Van Dyke (H. B.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 166-167.

Free iodin and iodate iodin cause only a very slight increase in iodin in the thyroid and thyroxin practically none, whereas iodides are markedly absorbed. **Adrenalectomy** of from one to six hours standing had no appreciable effect on the rate of acute absorption of iodide iodin.—G. E. B.

Thyroid function in vitamin B deficiency (Die Funktion der Thyreoidea bei Mangel an Vitamin B). Verzár (F.) & Vásárhelyi (B.), Arch. f. d. ges. Physiol. (Berl.), 1924, **206**, 675-687.

The respiration of surviving muscle is markedly increased by

different thyroid preparations and Ringer extracts of thyroid. On the average oxygen consumption of muscle from normal pigeons is increased by an extract of normal thyroid by 39%, that of muscle from pigeons on B-deficient diet by the same extract by 27%, while the thyroids of polyneuritic pigeons will increase the oxygen consumption of normal muscles only by about 7%. Hence the internal secretion causing this increased oxidation is decreased in polyneuritic pigeons. Normal thyroid extract increases the sugar consumption of the surviving normal rabbit hearts, and to a greater extent of polyneuritic rabbit hearts, but the thyroids of such polyneuritic rabbits have no effect on sugar consumption of the normal rabbit heart. Hence the decrease in metabolism of animals on a B-deficient diet can probably be ascribed to thyroid hypofunction.

—A. T. C.

The thyroxin and tryptophane content of the diseased thyroid gland and the iodin compound in desiccated thyroid. Weir (J. F.), Am. J. M. Sc. (Phila.), 1925, **169**, 860-865.

The thyroxin content of 24 exophthalmic goiters and 13 adenomatous goiters was determined. There were no characteristic variations from the normal in the adenomatous glands. In contrast to the low total iodin content and the low percentage of total iodin as thyroxin iodin reported to exist in exophthalmic glands by Wilson and Kendall, this series showed a total iodin of 2.58 mg. for each gm. (0.26%), of which an average of 43% was as thyroxin iodin—which are much higher figures. This is due to the preoperative administration of Lugol's solution to these patients and is a chemical criterion which agrees with the clinical improvement of the patients. No parallelism existed between the thyroxin content and basal metabolic rate. The average tryptophane content of 52 glands was 29.6 mg. for each gram of dried gland (approximately 3%). This is much higher than the tryptophane content of casein. No characteristic variations according to type of disease or thyroxin content were observed. The iodin compound in desiccated thyroid is not destroyed by boiling in strong alkali for 3 hours. The iodin not present as thyrotoxin under these conditions is not broken off as iodin.

The pathological classification of goiter. Williamson (G. S.), & Pearse (I. H.), J. Path. & Bacteriol. (Edinb.), 1925, **28**, 361-387. 10 plates.

The authors present a new classification of goiters based upon their own novel conception of the structure of the thyroid gland. They believe that "the functional gland-unit of the thyroid organ is essentially a lymphatic sinusoid in which float columns of epithelium enmeshed in a highly specialized plexus of blood capillaries"; and that the secretion of the thyroid is produced and stored in a specific fashion and is not the same as colloid. On the basis of this new con-

ception of the morphology and function of the thyroid, known pathological entities in this gland are referred to their point of departure from the normally functioning organ. "Hyperthyroidism" is dysthyroidism with a definite histological basis. Graves' disease is of two types: primary, associated with adenoid goiter; and secondary, with primary arterio-capillary sclerosis of the gland; in both forms it is something more than a simple dysthyroidism. Vesicular goiter is a distinct entity, is the histological obverse of adenoid goiter, and is probably a true hypothyroidism. "Adeno-parenchymatous" goiter is distinct from vesicular goiter, though the two types together constitute the class termed endemic goiter. Under hyperplastic goiter two states are defined—one referable to an anatomical deficiency, the simple type; and the other to a physiological deficiency, the lymphadenoid type. Myxoedema has a characteristic histopathology and is not a mere incidental atrophy of the thyroid gland.—J. P. S.